A 24-year-old man comes to the oncology clinic for a follow-up visit. The patient was diagnosed with Hodgkin lymphoma 4 months ago and received combination chemotherapy. He has had a nonproductive cough and shortness of breath with exertion over the past 2 weeks. On examination, there is no jugular venous distension or pedal edema. Heart sounds are normal with no murmurs. Lung auscultation reveals bilateral fine inspiratory crackles. Chest radiograph shows bilateral reticular interstitial opacities. Pulmonary function testing shows a restrictive pattern with decreased diffusion capacity for carbon monoxide. Chest x-ray and pulmonary function testing prior to the initiation of chemotherapy were normal. Which of the following is the most likely mechanism of action of the medication causing this patient's current symptoms?

- A. Disrupts microtubule polymerization causing M-phase arrest
- B. Impairs DNA synthesis by inhibiting thymidylate synthase
- C. Induces free radical formation and DNA strand breaks
- D. Inhibits topoisomerase II leading to DNA strand breaks
- E. Inhibits tyrosine kinases and cellular replication
- F. Produces cell-cycle arrests and apoptosis by inhibiting proteasomes

Submit

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- A. Disrupts microtubule polymerization causing M-phase arrest (6%)
- B. Impairs DNA synthesis by inhibiting thymidylate synthase (9%)
- ✓ C. Induces free radical formation and DNA strand breaks (72%)
- D. Inhibits topoisomerase II leading to DNA strand breaks (4%)
- E. Inhibits tyrosine kinases and cellular replication (3%)
- F. Produces cell-cycle arrests and apoptosis by inhibiting proteasomes (4%)

Omitted
Correct answer
C

72%
Answered correctly

33 secs
Time Spent

05/09/2020
Last Updated

Explanation

Specific toxicities of common chemotherapeutic agents		
Chemotherapy agent	Mechanism of Action	Toxicity

Specific toxicities of common chemotherapeutic agents		
Chemotherapy agent	**Mechanism of Action**	**Toxicity**
Anthracyclines (eg, doxorubicin)	• Binds with topoisomerase II to cleave DNA • Binds with iron to generate free radicals	• Dilated cardiomyopathy
Bleomycin	• Induces free radical formation	• Pulmonary fibrosis
Cisplatin	• Cross-links DNA to inhibit DNA synthesis	• Nephrotoxicity • Ototoxicity • Peripheral neuropathy
Cyclophosphamide	• Cross-links DNA to inhibit DNA synthesis	• Hemorrhagic cystitis • Bladder cancer
Paclitaxel	• Inhibits microtubule disassembly	• Neuropathy
Vincristine/ vinblastine	• Binds beta-tubulin to inhibit microtubule formation	• Neuropathy

Bleomycin is commonly used in the treatment of Hodgkin lymphoma and germ cell tumors; it exerts an antineoplastic effect by binding with iron and oxygen molecules to create **free radicals** that cause **DNA strand breaks**. Lung toxicity, usually in the form of **pulmonary fibrosis**, is the most clinically important adverse effect of the drug.

Toxicity from bleomycin likely results from oxidative free-radical damage to healthy tissue, leading to a cycle of tissue damage and repair. The lungs are particularly susceptible because they lack bleomycin hydrolase, an enzyme that helps inactivate bleomycin in other tissues. Patients who develop lung toxicity typically experience **dyspnea**, **nonproductive cough**, and crackles on lung auscultation within 6 months following initiation of therapy. Bibasilar interstitial opacities are typically seen on chest x-ray, and spirometry demonstrates reduced FVC with relatively preserved FEV1, consistent with a **restrictive pattern**. In addition, there is **reduced diffusion capacity for carbon monoxide (DLCO)** due to impaired gas exchange across an inflamed or fibrosed interstitium.

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(Choice A) Vinka alkaloids (eg, vincristine, vinblastine) bind to beta-tubulin to disrupt microtubule polymerization and prevent mitotic cell division. Peripheral neuropathy is a common adverse effect of these drugs.

(Choice B) 5-fluoruracil inhibits thymidylate synthase to impair DNA synthesis. Bone marrow suppression (eg, anemia, neutropenia) can occur.

(Choice D) Etoposide inhibits topoisomerase II to cause DNA strand breaks, and is commonly associated with bone marrow suppression. Anthracyclines (eg, doxorubicin) also exert at least part of their antineoplastic effect by binding to topoisomerase II and can cause cardiotoxicity that manifests as dilated cardiomyopathy.

(Choice E) The tyrosine kinase inhibitors imatinib and erlotinib are used to treat chronic myelogenous leukemia and lung cancer, respectively. These drugs disrupt cellular replication and commonly cause diarrhea and skin rash.

(Choice F) Proteasome inhibitors (eg, bortezomib) are used in the treatment of multiple myeloma. These drugs can cause bone marrow suppression and sometimes peripheral neuropathy.

Educational objective:
Bleomycin is an antineoplastic agent that binds to iron and oxygen molecules to create free radicals that cause DNA strand breaks. The most clinically important adverse effect of bleomycin is lung toxicity, usually manifesting as pulmonary fibrosis. Patients develop dyspnea and nonproductive cough, and pulmonary function testing shows a restrictive pattern with reduced diffusion capacity for carbon monoxide (DLCO).

References

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Bleomycin is an antineoplastic agent that binds to iron and oxygen molecules to create free radicals that cause DNA strand breaks. The most clinically important adverse effect of bleomycin is lung toxicity, usually manifesting as pulmonary fibrosis. Patients develop dyspnea and nonproductive cough, and pulmonary function testing shows a restrictive pattern with reduced diffusion capacity for carbon monoxide (DLCO).

References

- Bleomycin-induced pulmonary toxicity.

Pharmacology	Hematology & Oncology	Interstitial lung disease
Subject	System	Topic

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A 57-year-old man comes to the emergency department due to fevers and painful mouth ulcers. He recently began methotrexate therapy for psoriasis. However, the patient has mistakenly taken the medication daily instead of 3 times a week. His past medical history is also significant for hypertension and chronic kidney disease. Temperature is 38.1 C (100.6 F). Examination reveals multiple aphthous ulcers in the oral pharynx. A complete blood cell count is as follows:

Hemoglobin	10.4 g/dL
Platelets	120,000/mm^3
Leukocytes	2,800/mm^3

Which of the following is the best next step in management?

- A. Allopurinol
- B. Amifostine
- C. Dexrazoxane
- D. Filgrastim
- E. Folinic acid
- F. Mesna
- G. Ondansetron

Submit

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Hemoglobin	10.4 g/dL
Platelets	120,000/mm^3
Leukocytes	2,800/mm^3

Which of the following is the best next step in management?

- A. Allopurinol (3%)
- B. Amifostine (1%)
- C. Dexrazoxane (1%)
- D. Filgrastim (10%)
- ✓ E. Folinic acid (76%)
- F. Mesna (5%)
- G. Ondansetron (1%)

Omitted
Correct answer
E

76%
Answered correctly

03 secs
Time Spent

05/03/2020
Last Updated

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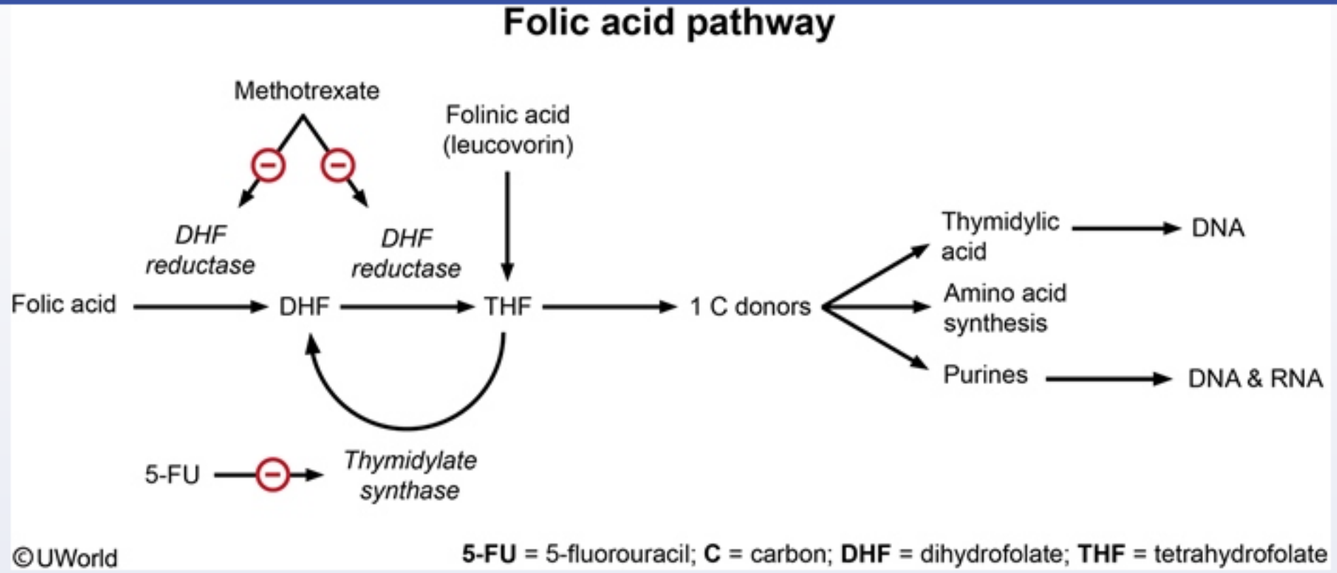

Methotrexate (MTX) is a folic acid analog that **inhibits dihydrofolate reductase** (DHFR), the enzyme that converts dietary folic acid to tetrahydrofolate (THF), through direct competition. THF is a single-carbon group donor in the synthesis of purines and thymidylic acid (which contributes to pyrimidine formation). MTX functions as a chemotherapeutic agent through **inhibition of DNA synthesis** and as an anti-psoriasis agent through immunomodulatory effects on activated T cells. However, MTX causes death of all **rapidly dividing** cells, particularly those of the **gastrointestinal tract** (GI) mucosa (explaining this patient's **aphthous ulcers**) and **bone marrow** (explaining this patient's **pancytopenia**).

Folinic acid (leucovorin) can reverse MTX toxicity if given early. It serves as a reduced form of folic acid thought **not** to require DHFR to be converted to THF and is therefore unaffected by MTX. Leucovorin is administered following high-dose MTX as part of a chemotherapeutic plan in which it serves to **rescue** bone marrow, and GI and other mucosal cells from MTX toxicity. In addition, when used in combination with 5-fluorouracil (**5-FU**), leucovorin **potentiates** the cytotoxic action of 5-FU (by binding thymidylate synthetase) and is frequently included in colorectal cancer chemotherapy regimens.

(Choice A) Allopurinol and its metabolite, oxipurinol, are predominantly noncompetitive inhibitors of xanthine oxidase. Allopurinol is used in the treatment of gout and for prevention of tumor lysis syndrome.

(Choice B) Amifostine is a cytoprotective free-radical scavenger used to decrease nephrotoxicity associated with platinum-containing and

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5-FU = 5-fluorouracil; **C** = carbon; **DHF** = dihydrofolate; **THF** = tetrahydrofolate

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(Choice C) Dexrazoxane is an iron-chelating agent that can prevent anthracycline-induced cardiotoxicity.

(Choice D) Filgrastim is a granulocyte colony-stimulating factor analog used to stimulate the proliferation and differentiation of granulocytes in patients with neutropenia.

(Choice F) Mesna prevents hemorrhagic cystitis due to cyclophosphamide or ifosfamide. Mesna binds acrolein, the toxic metabolite formed by these agents.

(Choice G) Ondansetron (a serotonin 5-HT_3 receptor inhibitor) is used to treat nausea and vomiting following chemotherapy.

Educational objective:
Folinic acid (leucovorin) can reverse the toxicity of methotrexate in non-cancerous cells in the gastrointestinal mucosa and bone marrow if administered at the appropriate time. Leucovorin serves as a reduced form of folic acid that does not require the action of dihydrofolate reductase.

gastrointestinal tract (GI) mucosa (explaining this patient's **aphthous ulcers**) and **bone marrow** (explaining this patient's **pancytopenia**).

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Pharmacology	Hematology & Oncology	Methotrexate
Subject	System	Topic

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A 12-year-old boy has prolonged oral bleeding immediately after a tooth extraction. Despite several interventions, the bleeding persists for hours and stops only after desmopressin (DDAVP) administration. The patient has several dental caries due to excessive juice intake and inconsistent oral hygiene. He has no other medical problems and takes no medications. His father and paternal grandmother have also had excessive bleeding after dental procedures. Review of systems is positive for mild bruising on his legs. Which of the following is the most likely therapeutic mechanism of desmopressin for this patient's condition?

A. Binding to renal tubular cell receptors

B. Increase in endothelial protein release

C. Increase in liver protein synthesis

D. Inhibition of fibrinolysis

E. Vascular smooth muscle contraction

Submit

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- A. Binding to renal tubular cell receptors (2%)
- ✓ B. Increase in endothelial protein release (65%)
- C. Increase in liver protein synthesis (8%)
- D. Inhibition of fibrinolysis (4%)
- E. Vascular smooth muscle contraction (19%)

Omitted
Correct answer
B

65%
Answered correctly

01 sec
Time Spent

04/25/2020
Last Updated

Explanation

Effects of desmopressin (DDAVP) therapy	
Mild hemophilia A & **Type 1 von Willebrand disease**	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding

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Mild hemophilia A & **Type 1 von Willebrand disease**	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding
Central diabetes insipidus & **Nocturnal enuresis**	Binds to V2 receptors in renal tubular cells, leading to increased aquaporin channels, increased water reabsorption & decreased urine output
vWF = von Willebrand factor.	

This patient likely has **von Willebrand disease (vWD)**, an **autosomal dominant** deficiency of von Willebrand factor (vWF). **vWF** is secreted by **endothelial cells** and circulates in multimers that are non-covalently attached to clotting factor VIII, increasing its stability. vWF is also responsible for augmenting platelet binding at endothelial injury sites, which helps in the formation of the initial **platelet plug**. Patients have **increased bruisability** and **mucosal bleeding** (eg, oropharyngeal, gastrointestinal, uterine). Common manifestations include prolonged bleeding during dental procedures and heavy menstrual periods.

Most patients do not require medical attention as vWD symptoms are typically mild. However, those who need treatment can receive **desmopressin** (or 1-desamino-8-d-arginine vasopressin [DDAVP]), a synthetic analog of vasopressin (ie, antidiuretic hormone [ADH]), which is normally released by the posterior pituitary. DDAVP increases vWF release from endothelial cells.

DDAVP also raises factor VIII levels and is used for the treatment of mild hemophilia A. Hemophilia is an X-linked coagulation disorder and is unlikely in this patient given the clear autosomal dominant pattern of inheritance (father and paternal grandmother).

(Choice A) DDAVP also acts as an ADH analogue by binding to V2 receptors in the renal tubular cells, which leads to increased aquaporin channels, increased water reabsorption, and decreased urine output. Due to this action, DDAVP can be used in the treatment of central diabetes insipidus and nocturnal enuresis.

(Choice C) Although most clotting factors are synthesized in the liver, vWF and factor VIII are produced in endothelial cells. DDAVP has no

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(Choice C) Although most clotting factors are synthesized in the liver, vWF and factor VIII are produced in endothelial cells. DDAVP has no known effect on liver protein synthesis.

(Choice D) Inhibition of fibrinolysis (breaking down fibrin in blood clots) can decrease the rate of clot breakdown and potentially slow heavy bleeding. Aminocaproic acid is an anti-fibrinolytic medication used to treat excessive postoperative bleeding. DDAVP has no effect on the fibrinolytic system.

(Choice E) Vascular smooth muscle cells are involved in blood pressure regulation, with contraction leading to higher blood pressure. Endogenous vasopressin acts via the V1 vasopressin receptor to raise blood pressure through vascular smooth muscle contraction. Although DDAVP is chemically similar to vasopressin, it has a minimal effect on the V1 vasopressin receptor.

Educational objective:
The von Willebrand factor (vWF) enhances clotting through both augmentation of platelet binding and stabilization of factor VIII. Patients with von

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Educational objective:
The von Willebrand factor (vWF) enhances clotting through both augmentation of platelet binding and stabilization of factor VIII. Patients with von Willebrand disease are deficient in functional vWF and present with increased bruisability and prolonged mucosal bleeding. Desmopressin can alleviate bleeding through endothelial release of vWF.

References

- Desmopressin (DDAVP) in the management of patients with congenital bleeding disorders.

Pharmacology	Hematology & Oncology	Von willebrand disease
Subject	System	Topic

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A 63-year-old man comes to the emergency department because of 1 hour of sudden-onset chest pain. He developed the pain after eating dinner and did not have relief with antacids. His other medical problems include hypertension, hyperlipidemia, and type 2 diabetes mellitus. In the emergency department, his blood pressure is 100/60 mm Hg, pulse is 100/min, and respirations are 18/min. His EKG shows ST-segment depression in the inferior leads, and his cardiac serum troponin T is positive. The following anticoagulants are being considered for treatment:

Anticoagulant	Molecular Weight
Unfractionated heparin	5000-30,000 u
Enoxaparin	3000-8000 u
Fondaparinux	Pentasaccharide

Which of the following anticoagulants is most effective in inactivating thrombin?

A. Enoxaparin

B. Fondaparinux

C. Unfractionated heparin

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Enoxaparin	3000-8000 u
Fondaparinux	Pentasaccharide

Which of the following anticoagulants is most effective in inactivating thrombin?

A. Enoxaparin (27%)

B. Fondaparinux (18%)

✓ C. Unfractionated heparin (54%)

Omitted
Correct answer
C

54%
Answered correctly

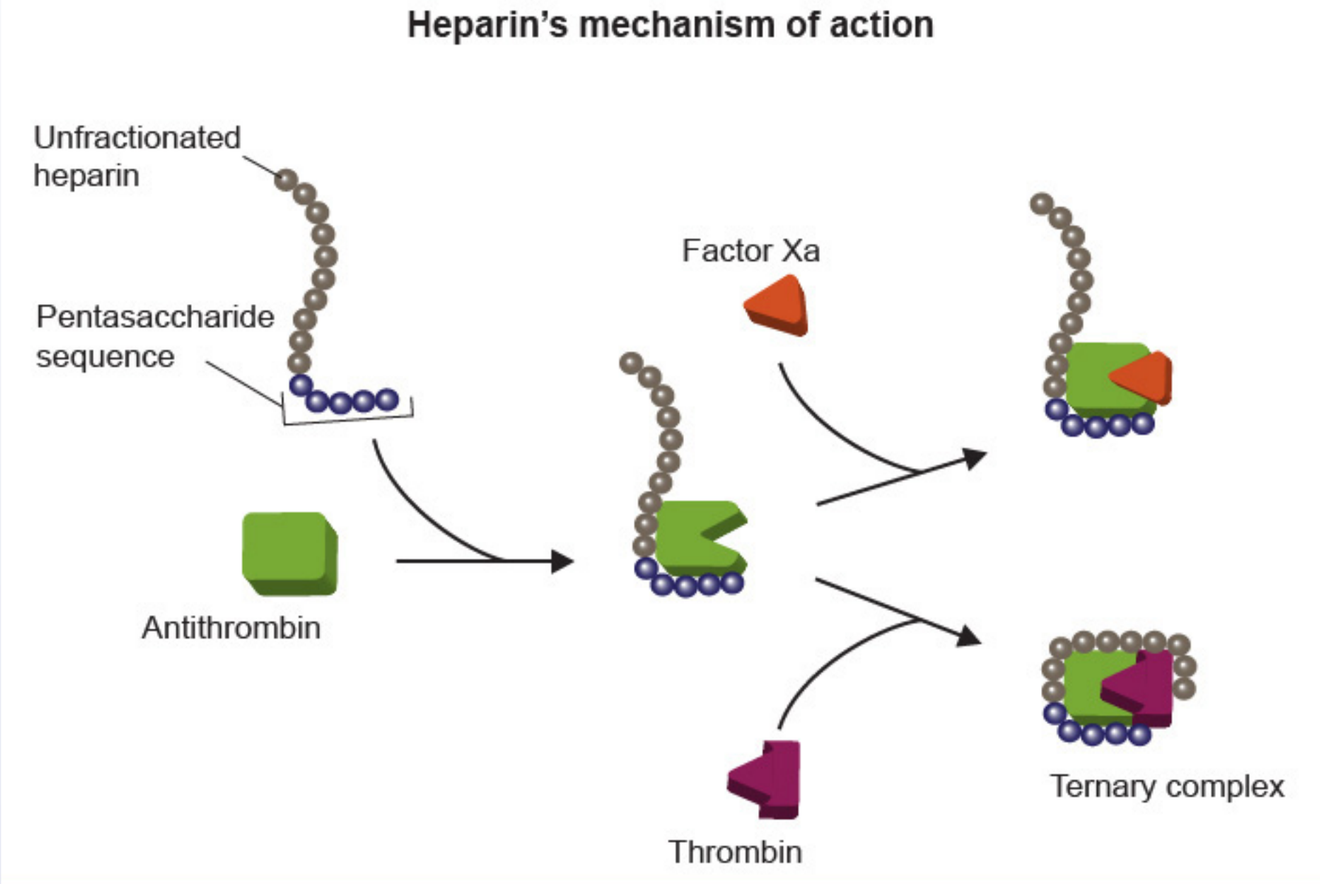
01 sec
Time Spent

06/20/2020
Last Updated

Explanation

This patient presents with findings consistent with acute coronary syndrome, with ongoing injury as evidenced by the positive troponin. An

This patient presents with findings consistent with acute coronary syndrome, with ongoing injury as evidenced by the positive troponin. An important component of therapy involves not only treating the existing clot but also preventing its propagation. The coagulation cascade amplifies the generation of thrombin, which activates platelets to form a plug and also helps convert fibrinogen to fibrin to reinforce the platelet plug. Antithrombin can inhibit both Factor Xa in the coagulation cascade and also thrombin.



Low-molecular-weight heparin

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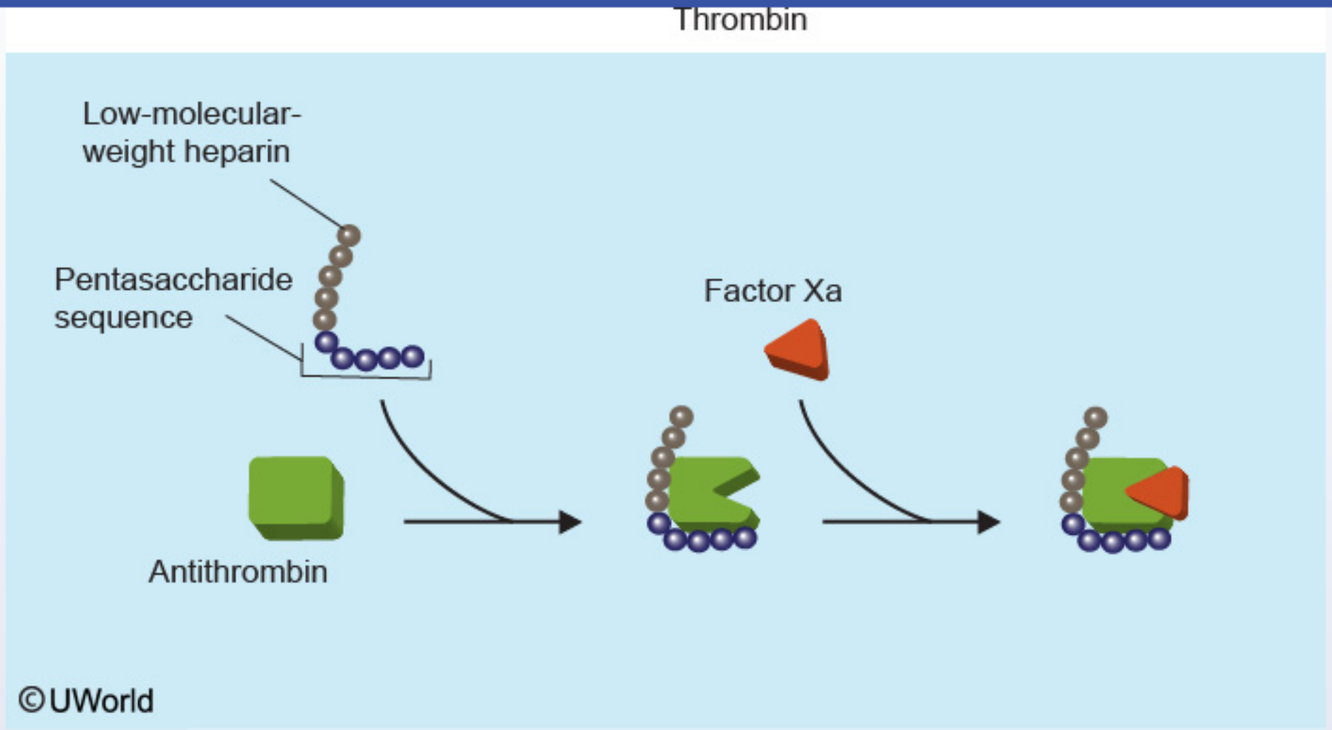

Both unfractionated heparin and low molecular weight heparin (LMWH) contain a pentasaccharide sequence that binds to antithrombin and causes a conformational change that increases its ability to inactivate Factor Xa. However, heparin must bind to both antithrombin and thrombin together to form a ternary complex to inactivate thrombin. Only unfractionated heparin (not LMWH) has a pentasaccharide chain long enough (>18 saccharide units) to bind to both antithrombin and thrombin. As a result, unfractionated heparin has equal activity against Factor Xa and thrombin, while LMWH has greater activity against Factor Xa than thrombin.

(Choice A) Enoxaparin is a low molecular weight heparin that has fewer of the required long saccharide units that bind to thrombin and less antithrombotic activity compared to unfractionated heparin.

(Choice B) Fondaparinux is a synthetic pentasaccharide Factor Xa inhibitor. It has none of the required long saccharide units that bind to thrombin and much lower antithrombin activity compared to unfractionated heparin.

Educational objective:

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Educational objective:
Both unfractionated heparin and LMWH can bind to antithrombin to increase its activity against Factor Xa. Only unfractionated heparin is able to bind to both antithrombin and thrombin to allow antithrombin to inactivate thrombin.

References

- Role of ternary complexes, in which heparin binds both antithrombin and proteinase, in the acceleration of the reactions between antithrombin and thrombin or factor Xa

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 36-year-old woman with mitral valve prolapse comes to the office due to dyspnea and is found to have severe mitral valve regurgitation. Two weeks later, the patient undergoes elective mechanical mitral valve replacement. Continuous heparin infusion and oral warfarin are initiated following the procedure. Coagulation studies during admission are as follows:

Postoperative day	1	2	3	4
INR	1.1	1.5	1.8	2.1
PTT(seconds)	72	76	74	78

The patient achieves the goal of INR ≥2.5 on postoperative day 5 and heparin infusion is discontinued. Which of the following likely caused the delay in achieving therapeutic INR in this patient?

A. Clotting factors generated before warfarin initiation

B. Formation of anti-platelet factor 4/heparin antibodies

C. High total body stores of vitamin K

D. Induction of an enzyme that metabolizes warfarin

E. Slow onset of steady-state drug concentration

Submit

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The patient achieves the goal of INR ≥2.5 on postoperative day 5 and heparin infusion is discontinued. Which of the following likely caused the delay in achieving therapeutic INR in this patient?

- ✓ A. Clotting factors generated before warfarin initiation (58%)
- B. Formation of anti-platelet factor 4/heparin antibodies (4%)
- C. High total body stores of vitamin K (9%)
- D. Induction of an enzyme that metabolizes warfarin (8%)
- E. Slow onset of steady-state drug concentration (19%)

Omitted
Correct answer
A

58%
Answered correctly

02 secs
Time Spent

03/25/2020
Last Updated

Explanation

Warfarin is a vitamin K antagonist that blocks **epoxide reductase** in the liver, leading to impaired vitamin K recycling. This depletes the reduced form of vitamin K, which is required for gamma carboxylation of **vitamin K–dependent clotting factors** (II, VII, IX, and X). In the absence of gamma carboxylation, vitamin K–dependent clotting factors cannot bind calcium or phospholipid membranes to induce coagulation.

Because warfarin inhibits gamma carboxylation of **new** vitamin K–dependent clotting factors, therapeutic efficacy is delayed until **preexisting clotting factors** in the plasma are consumed. Although INR tends to slowly increase in the first few days of administration due to the short half-life of factor VII (4-6 hours), full **therapeutic effect** does not typically occur for **3 days** due to the long half-life of **factor II**.

Warfarin also inhibits gamma carboxylation of the proteins C and S. Because these proteins exert an anticoagulant effect, the initiation of warfarin can be associated with an initial procoagulant state. However, once preexisting vitamin K–dependent clotting factors are consumed, an anticoagulant effect is established.

(Choice B) Anti-platelet factor 4/heparin antibodies cause heparin-induced thrombocytopenia, which typically arise 5-10 days after heparin initiation. This condition is marked by thrombocytopenia and a high risk of arterial and venous thrombosis, but would not result in a delay in therapeutic INR following warfarin administration.

(Choice C) Total body vitamin K is sufficient for several weeks; it does not contribute to a delay in warfarin efficacy. However, increased intake of foods rich in vitamin K (eg, green leafy vegetables) can lead to subtherapeutic INR due to increased vitamin K availability in the liver.

(Choice D) Warfarin is metabolized by the hepatic cytochrome P450 2C9 enzyme. Because many other medications induce or inhibit this enzyme, warfarin is susceptible to a wide range of drug interactions. However, the delay in achieving therapeutic INR is primarily due to the presence of preexisting clotting factors.

(Choice E) Warfarin reaches maximal plasma concentration approximately 90 minutes after administration. The delay in efficacy is due to the presence of preexisting clotting factors.

Educational objective:
Warfarin blocks epoxide reductase, which lowers the reduced form of vitamin K in the liver; this prevents gamma carboxylation of vitamin K–dependent clotting factors (II, VII, IX, and X). Because warfarin only blocks the generation of new clotting factors, therapeutic effect is delayed 3-5 days until preexisting clotting factors are consumed.

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Cancer cells from a 23-year-old male with testicular cancer demonstrate high sensitivity to etoposide. The etoposide-killed cancer cells show a high number of double-stranded DNA fractures. These fractures are due to dysfunction of which of the following?

A. Thymidylate synthase

B. Topoisomerase I

C. Topoisomerase II

D. Microtubules

E. Dihydrofolate reductase

Submit

Cancer cells from a 23-year-old male with testicular cancer demonstrate high sensitivity to etoposide. The etoposide-killed cancer cells show a high number of double-stranded DNA fractures. These fractures are due to dysfunction of which of the following?

- A. Thymidylate synthase (5%)
- B. Topoisomerase I (18%)
- ✓ C. Topoisomerase II (66%)
- D. Microtubules (6%)
- E. Dihydrofolate reductase (2%)

Omitted
Correct answer
C

66%
Answered correctly

01 sec
Time Spent

02/03/2020
Last Updated

Explanation

Etoposide is a semisynthetic derivative of the plant alkaloid podophyllotoxin, which targets topoisomerase II. The topoisomerases are enzymes that relieve the DNA supercoiling that occurs during DNA replication as a result of separation and unwinding of the double helix. Topoisomerase I makes single-stranded nicks to relieve negative supercoiling, while topoisomerase II induces transient breaks in both DNA strands simultaneously to relieve both positive and negative supercoiling. Etoposide and podophyllin specifically inhibit topoisomerase II's ability to seal the strand breaks it induces, causing chromosomal breaks to accumulate and eventual cell death. Two major uses of etoposide are in testicular cancer and small cell lung cancer. Podophyllin is used topically to treat genital warts.

(Choices A and E) Antimetabolites are medications that interfere with nucleotide metabolism, thus inhibiting incorporation of new nucleotides into

Explanation

Etoposide is a semisynthetic derivative of the plant alkaloid podophyllotoxin, which targets topoisomerase II. The topoisomerases are enzymes that relieve the DNA supercoiling that occurs during DNA replication as a result of separation and unwinding of the double helix. Topoisomerase I makes single-stranded nicks to relieve negative supercoiling, while topoisomerase II induces transient breaks in both DNA strands simultaneously to relieve both positive and negative supercoiling. Etoposide and podophyllin specifically inhibit topoisomerase II's ability to seal the strand breaks it induces, causing chromosomal breaks to accumulate and eventual cell death. Two major uses of etoposide are in testicular cancer and small cell lung cancer. Podophyllin is used topically to treat genital warts.

(Choices A and E) Antimetabolites are medications that interfere with nucleotide metabolism, thus inhibiting incorporation of new nucleotides into elongating DNA strands. For example, thymidylate synthase and dihydrofolate reductase are enzymes central to thymidine nucleotide synthesis. 5-Fluorouracil and 5-deoxyuridine are antimetabolites that inhibit thymidylate synthase, and methotrexate is an antimetabolite that inhibits dihydrofolate reductase.

(Choice B) Irinotecan and topotecan inhibit topoisomerase I, an enzyme that induces single-strand breaks in DNA to relieve negative supercoiling during replication.

(Choice D) Vinca alkaloids like vincristine and vinblastine bind tubulin monomers, disrupting the microtubules necessary for separating chromosome strands during mitosis. Taxanes like paclitaxel also cause microtubular dysfunction.

Educational Objective:
Etoposide is a chemotherapeutic agent that inhibits the sealing activity of topoisomerase II. Treatment with etoposide causes chromosomal breaks to accumulate in dividing cells, ultimately causing cell death.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 62-year-old woman is evaluated for refractory nausea and vomiting. She was recently diagnosed with ovarian cancer and underwent total hysterectomy with bilateral salpingo-oophorectomy and pelvic lymph node dissection. The patient was started on highly emetogenic adjuvant chemotherapy. Despite taking ondansetron around the clock, she continues to have nausea and vomiting. She has no abdominal pain or constipation. Vital signs are normal. Examination shows a well-healed abdominal scar. There is no tenderness or abnormal masses. Bowel sounds are normal. Additional therapy blocking which of the following receptors would most likely be helpful in this patient?

A. Endogenous opioid

B. Motilin

C. Neurokinin 1

D. Neuropeptide Y

E. Nicotinic acetylcholine

Submit

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- A. Endogenous opioid (16%)
- B. Motilin (14%)
- ✓ C. Neurokinin 1 (33%)
- D. Neuropeptide Y (24%)
- E. Nicotinic acetylcholine (10%)

Omitted
Correct answer
C

33%
Answered correctly

01 sec
Time Spent

05/18/2020
Last Updated

Explanation

Characteristics of antiemetic drugs		
Drug class	Examples	Clinical uses

Characteristics of antiemetic drugs

Drug class	Examples	Clinical uses
Antimuscarinics (anticholinergics)	• Scopolamine	Motion sickness Hyperemesis gravidarum (promethazine)
Antihistamines	• Diphenhydramine • Meclizine • Promethazine	
Dopamine receptor antagonists	• Prochlorperazine • Metoclopramide	Chemotherapy-induced emesis
Serotonin (5-HT_3) receptor antagonists	• Ondansetron • Granisetron	
Neurokinin 1 (NK1) receptor antagonists	• Aprepitant • Fosaprepitant	

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Vomiting is a reflex that can be activated by either humoral or neuronal stimuli. The **area postrema** in the fourth ventricle has a chemoreceptor trigger zone that can respond to many neurotransmitters, drugs, or toxins. The **nucleus tractus solitarius** (NTS) in the medulla receives information from the area postrema, gastrointestinal tract via the vagus nerve, vestibular system, and central nervous system (eg, meninges, hypothalamus). Neurons from the NTS project to other medullary nuclei and coordinate the vomiting process.

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The 5 major receptors involved in stimulating the vomiting reflex in the area postrema and adjacent vomiting center nuclei are M_1 muscarinic, D_2 dopaminergic, H_1 histaminic, 5-HT_3 serotonergic, and neurokinin 1 (NK1) receptors. **5-HT3 receptor antagonists** (eg, ondansetron) and dopamine receptor antagonists (eg, metoclopramide) are particularly helpful for chemotherapy-induced vomiting. When these do not control symptoms, **NK1 receptor antagonists** (prevent substance P release) can be considered; they prevent both acute vomiting and delayed emesis associated with chemotherapy.

(Choice A) Opioid receptor antagonists (eg, naltrexone) competitively bind opioid receptors to prevent action of endogenous or exogenous opioids. They are used mainly for opioid dependence.

(Choice B) Motilin regulates interdigestive migrating contractions. Erythromycin is a motilin receptor agonist used for gastroparesis.

(Choice D) Neuropeptide Y is a polypeptide neurotransmitter found in the central and autonomic nervous systems. It is thought to play a role in appetite and pain perception. Neuropeptide Y antagonists have been investigated as potential antiobesity drugs.

(Choice E) Nicotinic antagonists are primarily used for muscle paralysis during surgery. Some antihistamines (eg, promethazine, meclizine) and antimuscarinics (eg, scopolamine) have anticholinergic activity and inhibitory effects on both the vomiting center and vestibular apparatus (useful for motion sickness).

Educational objective:
Vomiting is a reflex regulated mainly by 5 receptors, including M_1 muscarinic, D_2 dopaminergic, H_1 histaminic, 5-HT_3 serotonergic, and neurokinin 1 (NK1) receptors. 5-HT_3 and NK1 receptor antagonists are particularly useful for chemotherapy-induced vomiting.

References

- Nausea, vomiting, and hiccups: a review of mechanisms and treatment.
- Neurokinin-1 receptor antagonists for chemotherapy-induced nausea and vomiting.

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A 67-year-old man is being evaluated for lower back pain and fatigue. His back pain worsens when he lies flat. His past medical history is unremarkable. Hemoglobin level is 8.5 mg/dL, serum creatinine is 2.2 mg/dL, and serum calcium is 10.6 mg/dL. After initial evaluation, the patient is treated with an infusion of a boronic acid-containing dipeptide that has a high affinity for the proteasome catalytic site. This treatment would most likely result in which of the following?

A. Amyloid plaque resorption

B. Cell apoptosis

C. Decreased inflammation

D. Decreased serum calcium levels

E. Interruption of IgG synthesis

Submit

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- A. Amyloid plaque resorption (15%)
- ✓ B. Cell apoptosis (34%)
- C. Decreased inflammation (15%)
- D. Decreased serum calcium levels (15%)
- E. Interruption of IgG synthesis (18%)

Omitted
Correct answer
B

34%
Answered correctly

01 sec
Time Spent

02/08/2020
Last Updated

Explanation

This patient with bone pain, fatigue, anemia, kidney disease, and hypercalcemia has **multiple myeloma** (MM). In MM, neoplastic B lymphocytes mature into plasma cells that typically synthesize large amounts of monoclonal immunoglobulin (Ig) or Ig fragments (eg, IgG light chains). As a result of this increased protein production, plasma cells are particularly susceptible to the effects of **proteasome inhibitors** such as bortezomib, a boronic acid-containing dipeptide.

Proteasomes act as recycling centers for proteins, breaking down misfolded, damaged, and cytotoxic proteins into their component building blocks for reuse in new proteins. Proteasome inhibition results in the accumulation of toxic intracellular proteins. In addition, proteasomes regulate the

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Proteasomes act as recycling centers for proteins, breaking down misfolded, damaged, and cytotoxic proteins into their component building blocks for reuse in new proteins. Proteasome inhibition results in the accumulation of toxic intracellular proteins. In addition, proteasomes regulate the balance of pro- and antiapoptotic proteins, and their inhibition leads to an excess of proapoptotic proteins. Both of these effects induce **apoptosis** of the malignant plasma cells.

(Choices A and E) MM leads to the production of large amounts of light chains (eg, IgG) that are commonly deposited in tissues ("light chain amyloidosis"). However, proteasome inhibitors do not directly impact IgG synthesis or amyloid plaque deposition or resorption.

(Choice C) Although corticosteroids such as dexamethasone are frequently part of the routine management of MM and decrease inflammation, proteasome inhibition is not their main mechanism of action.

(Choice D) Hypercalcemia of MM (likely primarily due to tumor-induced bone resorption) is treated with hydration, corticosteroids (mild hypercalcemia), and bisphosphonates (moderate to severe hypercalcemia). Proteasome inhibition would not directly affect serum calcium levels.

Educational objective:
In multiple myeloma, neoplastic plasma cells synthesize large amounts of monoclonal immunoglobulin or immunoglobulin fragments. These cells are particularly susceptible to proteasome inhibition due to the large amount of proteins that they manufacture. The resulting accumulation of toxic intracellular and proapoptotic proteins increases cellular apoptosis.

References

- Mechanism of action of proteasome inhibitors and deacetylase inhibitors and the biological basis of synergy in multiple myeloma.
- Proteasome inhibitors in multiple myeloma: 10 years later.
- Proteasome inhibitors in cancer therapy.

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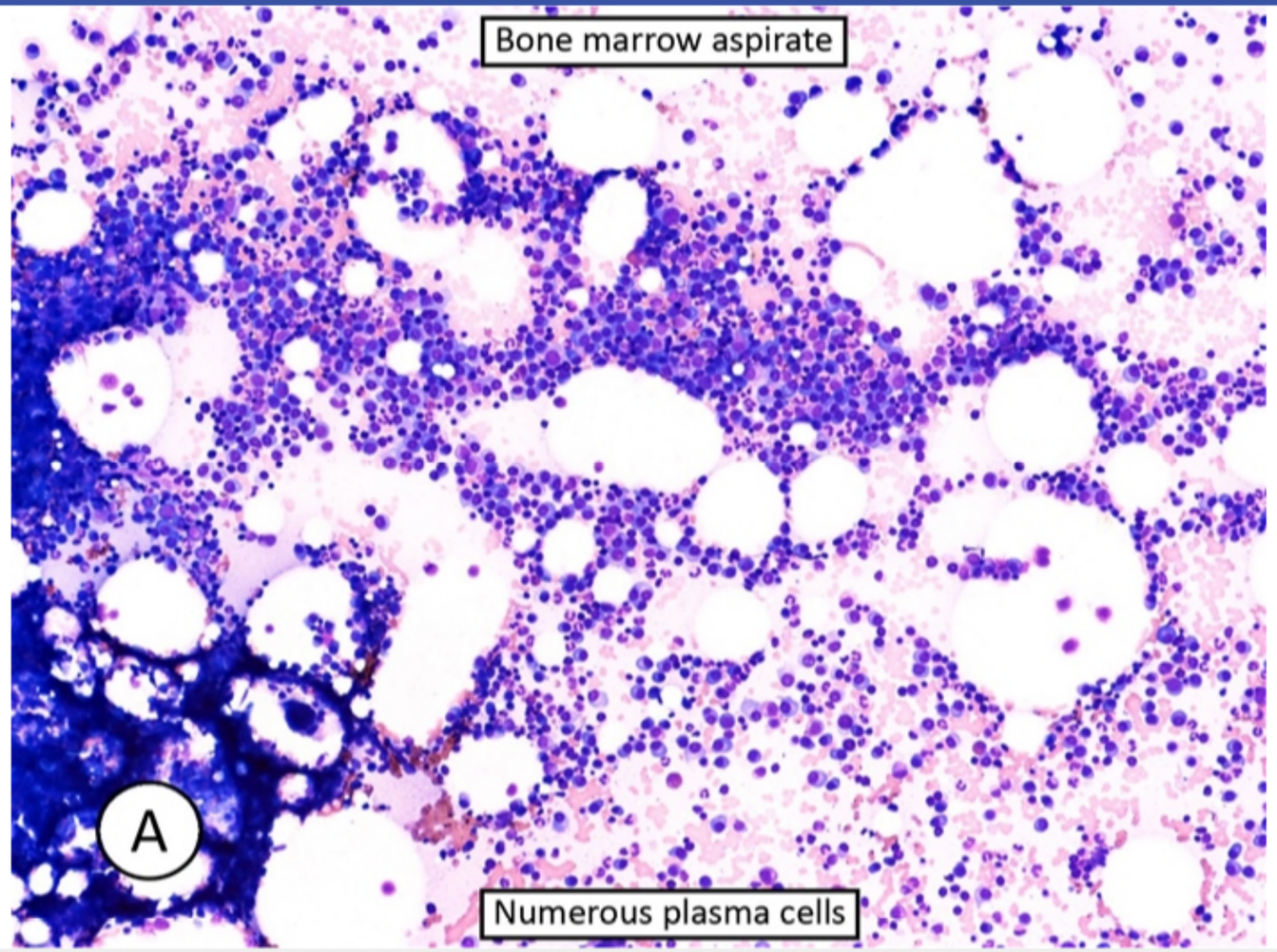
Exhibit Display



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A 55-year-old woman is diagnosed with metastatic breast cancer. The patient is treated with an opioid analgesic for bone pain that is well controlled during the first week of therapy. The following week, the analgesic dose becomes ineffective and the patient reports nausea, itching, and constipation. She has become very weak and is unable to walk due to the pain. The opioid dose is increased. The patient is concerned about side effects with higher dosages, noting that her son has a history of opioid dependence, and "I watched him suffer a lot of bad reactions." The physician explains the concept of tolerance to opioids and that high doses are commonly required to control pain. Over the next few weeks, the patient would likely experience which of the following?

A. Euphoria
B. Increased itching
C. Persistent nausea and vomiting
D. Respiratory depression
E. Sedation
F. Urinary retention
G. Worsening constipation

Submit

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

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- A. Euphoria (4%)
- B. Increased itching (1%)
- C. Persistent nausea and vomiting (2%)
- D. Respiratory depression (10%)
- E. Sedation (6%)
- F. Urinary retention (1%)
- ✓ G. Worsening constipation (73%)

Omitted
Correct answer
G

73%
Answered correctly

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Time Spent

05/09/2020
Last Updated

Explanation

Opioid therapy is the first-line treatment for chronic cancer pain, with effective management commonly requiring higher doses over prolonged

Explanation

Opioid therapy is the first-line treatment for chronic cancer pain, with effective management commonly requiring higher doses over prolonged periods. An increase in dosage is often necessary to maintain adequate pain control following the development of tolerance to analgesic effects. Tolerance to most opioid side effects is also expected to occur. However, tolerance to constipation and miosis does not readily occur, and **constipation** is the most **common** and **persistent opioid side effect**.

Opioids stimulate mu receptors in the gastrointestinal tract, causing decreased secretions and gastric motility. Normal bowel function rarely resumes. Patients who require prolonged opioid therapy should receive a **prophylactic bowel regimen** (increased fluid intake, dietary fiber, and laxatives) to minimize constipation.

(Choice A) Opioids can produce significant euphoria, mood alterations, and rewarding pleasurable effects. The mechanism of euphoria and rewarding properties may involve dopaminergic pathways in the nucleus accumbens. Tolerance to euphoric effects develops rapidly, underlying the addictive potential of this medication class.

(Choice B) In most cases, opioid-induced pruritus is mild and tolerance develops.

(Choice C) Nausea with or without vomiting is a common side effect during initiation of opioid therapy, but tolerance develops within days and persistent nausea is uncommon. Opioids stimulate the chemoreceptor trigger zone, leading to emesis.

(Choice D) Respiratory depression is the most serious, yet rare, side effect of opioid therapy. Opioids depress respiration by reducing responsiveness of brainstem respiratory centers to increased levels of carbon dioxide. Patients who take opioids regularly are unlikely to develop respiratory depression as tolerance to this side effect develops rapidly.

(Choice E) Sedation typically occurs during initiation of therapy and usually disappears after several days. It is not unusual for patients to be drowsy and sleep more during the first days of therapy.

(Choice F) Opioids block urinary voiding reflexes and also increase sphincter tone and bladder volume. This results in an antidiuretic effect and urinary retention. Tolerance to these effects develops rapidly.

Educational objective:
Chronic opioid use leads to the development of tolerance to analgesic effects and most side effects, with the exception of constipation and miosis.

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Educational objective:
Chronic opioid use leads to the development of tolerance to analgesic effects and most side effects, with the exception of constipation and miosis. To prevent bowel complications, it is recommended that patients be treated prophylactically with adequate fluid intake and daily laxatives.

References

- Gastrointestinal side effects in chronic opioid users: results from a population-based survey.
- Opioid complications and side effects.

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Pharmacology	Hematology & Oncology	Opioids
Subject	System	Topic

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A 63-year-old man comes to the hospital due to sudden onset chest pain and dyspnea. He has a history of glioblastoma multiforme, for which he has been undergoing radiation treatment. His temperature is 36.1 C (97 F), blood pressure is 110/80 mm Hg, pulse is 118/min, and respirations are 26/min. Pulse oximetry shows 90% on room air. A CT pulmonary angiogram demonstrates a left-sided pulmonary embolism. The patient is started on continuous unfractionated heparin infusion. Several hours later, the patient begins to experience severe headache and quickly becomes unconscious. A CT of the head reveals bleeding into the tumor. After stopping the heparin infusion, administration of which of the following is indicated for immediate anticoagulant reversal?

A. Fresh frozen plasma
B. Platelets
C. Protamine
D. Prothrombin complex concentrate
E. Tranexamic acid
F. Vitamin K

Submit

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- A. Fresh frozen plasma (14%)
- B. Platelets (1%)
- ✓ C. Protamine (78%)
- D. Prothrombin complex concentrate (3%)
- E. Tranexamic acid (1%)
- F. Vitamin K (1%)

Omitted
Correct answer
C

78%
Answered correctly

01 sec
Time Spent

06/16/2020
Last Updated

Explanation

Unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) are commonly used anticoagulants in the hospital setting. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III (ATIII). Activated partial thromboplastin time (aPTT) is measured to

	Warfarin overdose	Heparin overdose
Vitamin K	Effective (takes days)	Ineffective
FFP	Effective (contains all blood clotting factors & proteins)	Ineffective (contains antithrombin III → enhances heparin effect)
Protamine	Ineffective	Effective (heparin-specific antidote)

FFP = fresh frozen plasma.

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Unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) are commonly used anticoagulants in the hospital setting. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III (ATIII). Activated partial thromboplastin time (aPTT) is measured to monitor the therapeutic effect of heparin. Bleeding and heparin-induced thrombocytopenia are serious complications of heparin therapy. **Bleeding** due to heparin toxicity is treated with **protamine** sulfate, a specific antagonist. Protamine sulfate is a peptide that binds to heparin, forming a complex that has no anticoagulant activity. Although protamine is often used in the management of LMWH toxicity, it does not completely reverse the anti-Xa activity of LMWH.

Vitamin K is used for reversal of **warfarin** overdose but requires new synthesis of coagulation factors. As a result, its full effect takes time to manifest. For this reason, in the setting of acute life-threatening bleeding due to warfarin, fresh frozen plasma (**FFP**) (contains all blood proteins and clotting factors) should be given. However, FFP is **not** useful for heparin overdose as it contains ATIII, which can further potentiate the effects of heparin. **Prothrombin complex concentrates** (PCCs), which contain the vitamin K-dependent factors II, VII, IX, and X, can be used to treat bleeding due to warfarin (not heparin) overdose **(Choices A, D, and F)**.

(Choices B and E) Platelet function is not affected by warfarin therapy. Aminocaproic acid and tranexamic acid inhibit fibrinolysis by inhibiting plasminogen activation.

Educational objective:

FFP	clotting factors & proteins)	→ enhances heparin effect)
Protamine	Ineffective	Effective (heparin-specific antidote)

FFP = fresh frozen plasma.

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Unfractionated heparin (UFH) and low-molecular weight heparins (LMWHs) are commonly used anticoagulants in the hospital setting. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III (ATIII). Activated partial thromboplastin time (aPTT) is measured to monitor the therapeutic effect of heparin. Bleeding and heparin-induced thrombocytopenia are serious complications of heparin therapy. **Bleeding** due to heparin toxicity is treated with **protamine** sulfate, a specific antagonist. Protamine sulfate is a peptide that binds to heparin, forming a complex that has no anticoagulant activity. Although protamine is often used in the management of LMWH toxicity, it does not completely reverse the anti-Xa activity of LMWH.

Vitamin K is used for reversal of **warfarin** overdose but requires new synthesis of coagulation factors. As a result, its full effect takes time to manifest. For this reason, in the setting of acute life-threatening bleeding due to warfarin, fresh frozen plasma (**FFP**) (contains all blood proteins and clotting factors) should be given. However, FFP is **not** useful for heparin overdose as it contains ATIII, which can further potentiate the effects of heparin. **Prothrombin complex concentrates** (PCCs), which contain the vitamin K-dependent factors II, VII, IX, and X, can be used to treat bleeding due to warfarin (not heparin) overdose **(Choices A, D, and F)**.

(Choices B and E) Platelet function is not affected by warfarin therapy. Aminocaproic acid and tranexamic acid inhibit fibrinolysis by inhibiting plasminogen activation.

Educational objective:
Protamine sulfate binds to heparin, causing chemical inactivation. Vitamin K and fresh frozen plasma can be used to reverse warfarin effects.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 12-year-old boy is evaluated due to fever, fatigue, and easy bruising. Physical examination shows pallor, generalized lymphadenopathy, and bone tenderness. Laboratory evaluation reveals anemia, thrombocytopenia, and leukocytosis with atypical lymphoblasts. Bone marrow biopsy is consistent with acute lymphoblastic leukemia. The patient is treated with combination chemotherapy, and 6-mercaptopurine is administered for maintenance of remission. Which of the following enzymes inactivates this drug?

A. Adenosine deaminase
B. Dihydrofolate reductase
C. Hypoxanthine-guanine phosphoribosyltransferase
D. Monoamine oxidase
E. P-450 mixed-function oxidase
F. Topoisomerase II
G. Xanthine oxidase

Submit

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- A. Adenosine deaminase (6%)
- B. Dihydrofolate reductase (4%)
- C. Hypoxanthine-guanine phosphoribosyltransferase (13%)
- D. Monoamine oxidase (1%)
- E. P-450 mixed-function oxidase (4%)
- F. Topoisomerase II (0%)
- ✓ G. Xanthine oxidase (69%)

Omitted
Correct answer
G

69%
Answered correctly

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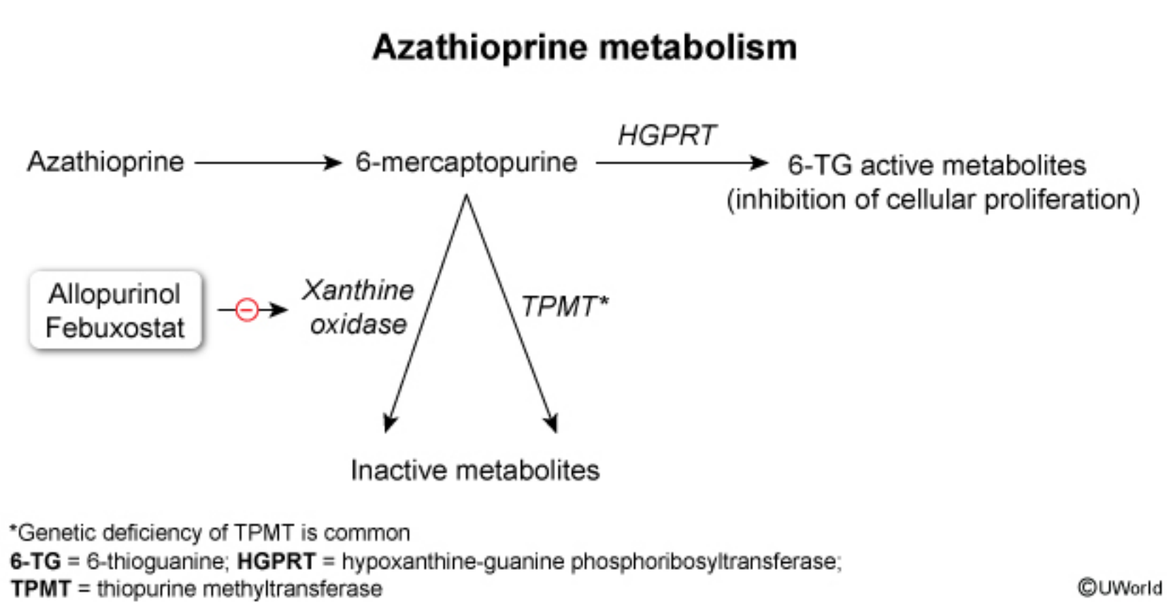
04/20/2020
Last Updated

Explanation

Azathioprine metabolism

HGPRT

Explanation



6-mercaptopurine (6-MP) can be administered directly or in its prodrug form (ie, **azathioprine**). Following ingestion, 6-MP is converted by hypoxanthine-guanine phosphoribosyltransferase (HGPRT) into 6-thioguanine (6-TG) active metabolites **(Choice C)**. The 6-TG metabolites are purine analogues that act as false nucleotides to disrupt DNA and RNA synthesis and inhibit the proliferation of hematopoietic cells, a useful effect in the treatment of autoimmune disease, organ transplant rejection, and some types of cancer (eg, leukemia).

6-MP is **metabolized into inactive metabolites** by 2 different enzymes, **xanthine oxidase** and **thiopurine methyltransferase** (TPMT), both of which are clinically important. Coadministration of 6-MP with a xanthine oxidase inhibitor (eg, allopurinol, febuxostat) slows the inactivation of 6-MP and shunts metabolism toward the production of 6-TG active metabolites; therefore, the dose of 6-MP must be significantly reduced. In addition, roughly 12% of the population has a genetic mutation resulting in low or absent activity of TPMT, creating a high risk of toxicity with the administration of 6-MP. Therefore, some clinicians recommend that patients undergo genetic testing for TPMT activity prior to initiating 6-MP (or azathioprine) therapy.

(Choice A) Adenosine deaminase (ADA) converts adenosine to inosine as part of purine metabolism. This enzyme is deficient in severe

TPMT = thiopurine methyltransferase

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(Choice A) Adenosine deaminase (ADA) converts adenosine to inosine as part of purine metabolism. This enzyme is deficient in severe combined immunodeficiency but may be overexpressed in some malignancies. Cladribine, which is used in the treatment of hairy cell leukemia, is a cytotoxic purine analogue resistant to degradation by ADA.

(Choice B) Methotrexate is used in the treatment of cancer and rheumatologic disease. It inhibits dihydrofolate reductase, thereby blocking the conversion of dihydrofolate to tetrahydrofolate and disrupting the synthesis of thymidine and, to a lesser extent, purines.

(Choice D) Monoamine oxidase inhibitors are used in the treatment of atypical depression; these agents inhibit degradation of the neurotransmitters norepinephrine, dopamine, and serotonin.

(Choice E) Cyclophosphamide, used to treat many types of cancer, requires bioactivation by the cytochrome P-450 mixed-function oxidase system.

(Choice F) Topoisomerase II is inhibited by the chemotherapeutic agents etoposide and teniposide.

Educational objective:
6-mercaptopurine (6-MP) is an immunosuppression drug that is inactivated by 2 enzymes, xanthine oxidase and thiopurine methyltransferase. Reduced function of either enzyme causes increased levels of the active metabolites of 6-MP, leading to increased immunosuppression and risk of toxicity.

addition, roughly 12% of the population has a genetic mutation resulting in low or absent activity of TPMT, creating a high risk of toxicity with the administration of 6-MP. Therefore, some clinicians recommend that patients undergo genetic testing for TPMT activity prior to initiating 6-MP (or azathioprine) therapy.

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References

- Implementation of TPMT testing.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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Researchers are conducting a study to determine the effectiveness of a novel humanized monoclonal antibody in patients with metastatic colorectal cancer. This medication works by binding to the programmed cell death-1 receptor on T cells to block its ligands from binding. They find this therapy is most effective in patients with a high degree of microsatellite instability or defects in DNA mismatch repairs. Which of the following best explains the favorable drug effect in this subset of patients?

A. Higher expression of P-glycoprotein

B. Higher number of cancer neoantigens

C. Higher rate of *KRAS* mutations

D. Higher rate of *p53* mutations

E. More intense desmoplastic reaction

Submit

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- A. Higher expression of P-glycoprotein (15%)
- ✓ B. Higher number of cancer neoantigens (34%)
- C. Higher rate of *KRAS* mutations (18%)
- D. Higher rate of *p53* mutations (26%)
- E. More intense desmoplastic reaction (5%)

Omitted
Correct answer
B

34%
Answered correctly

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Time Spent

06/13/2020
Last Updated

Explanation

The genetic mutations that drive oncogenesis also create unique proteins not found in healthy cells. Antigens from these proteins (**neoantigens**) are displayed on the surface of tumor cells and may be subsequently recognized by patrolling cytotoxic T cells as "not-self" and destroyed. Cancers with defects in **mismatch repair proteins** and high microsatellite instability (reflecting DNA polymerase errors during cellular replication) are particularly susceptible to **immune recognition** because they rapidly accumulate mutations and generate approximately 20-fold more neoantigens than tumor cells that have normal mismatch repair.

Cancer cells use a wide range of mechanisms to thwart cytotoxic T-cell detection, including:

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- Downregulating cell surface receptors involved in immune recognition. For instance, decreased expression of the major histocompatibility complex leads to decreased neoantigen presentation on the surface of the cell.
- Overexpressing cell surface proteins that inhibit the immune response. For instance, cancer cells can overexpress programmed death-ligand 1 (PD-L1), which binds to the programmed cell death-1 (PD-1) receptor on the T-cell surface and inhibits the cytotoxic T-cell response (T-cell exhaustion).

Cancer cells that overexpress PD-L1 are less susceptible to cytotoxic T-cell–mediated destruction (enhanced T-cell exhaustion). These tumors can be treated with **monoclonal antibodies** that block the PD-1 receptor on T cells (eg, pembrolizumab, nivolumab) or the PD-1 ligand on cancer cells (eg, atezolizumab). Treatment stimulates the cytotoxic T-cell response; it is particularly effective against tumors with large quantities of neoantigens (eg, those with deficits in mismatch repair) because these tumors are particularly susceptible to recognition as "not-self."

(Choice A) P-glycoprotein is a multidrug transporter that can be used by cancer cells to pump cytotoxic chemotherapy out of the cell.

(Choice C) *KRAS* is a proto-oncogene that is part of the signaling pathway for the epidermal growth factor receptor. Activating mutations in *KRAS* lead to unregulated cellular growth. Tumors with activating mutations to *KRAS* are resistant to monoclonal antibodies against epidermal growth factor receptor because they have an activating mutation in a downstream signal.

(Choice D) p53 is a tumor-suppressor protein that inhibits cellular replication when DNA is damaged and induces apoptosis. Mutations to *p53* can lead to unregulated cellular growth and may inhibit cytotoxic chemotherapy–mediated cancer cell apoptosis.

(Choice E) Desmoplasia (dense fibrosis) around a tumor can reduce the ability of cytotoxic chemotherapy to enter cancer cells.

Educational objective:

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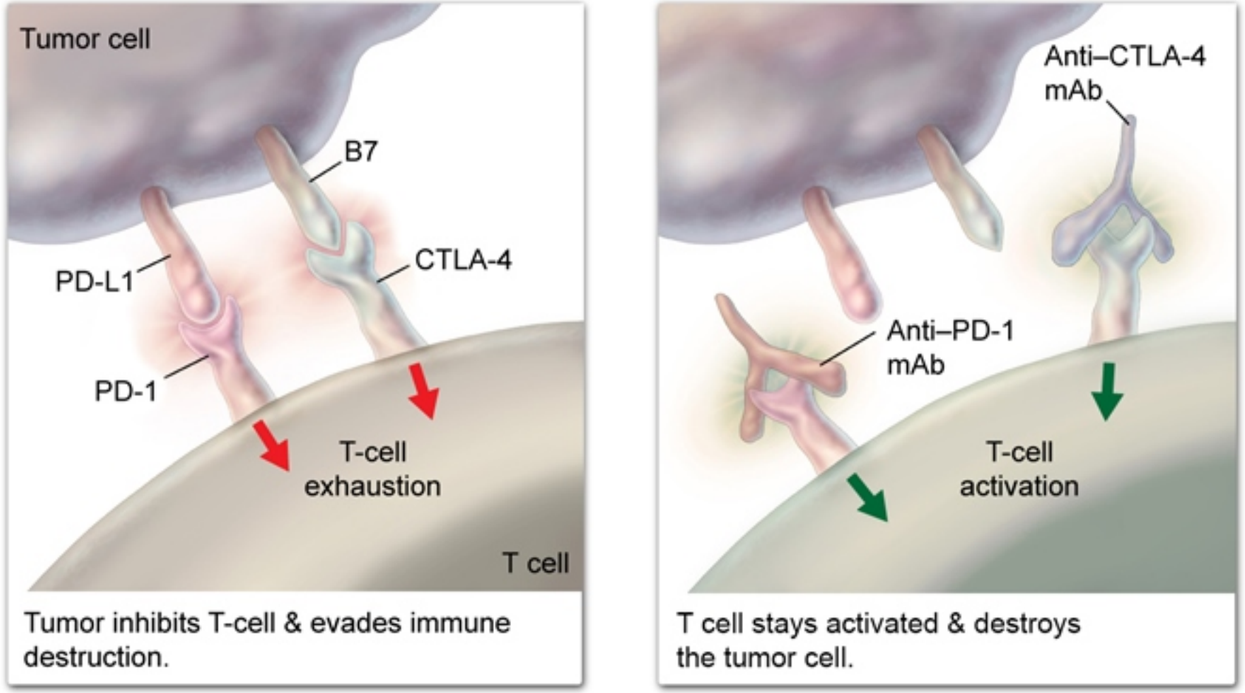
Educational objective:
Cancer cells avoid immune recognition by overexpressing programmed death-ligand 1 (PD-L1), which binds to the programmed cell death-1 (PD-1) receptor on cytotoxic T cells and inhibits their response (T-cell exhaustion). Monoclonal antibodies that block PD-L1 and PD-1 are effective

Downregulating cell surface receptors involved in immune recognition. For instance, decreased expression of the major histocompatibility

Exhibit Display

Cancer immunotherapy: anti–PD-1 & anti–CTLA-4 antibodies



CTLA-4 = cytotoxic T-lymphocyte–associated protein 4; **mAb** = monoclonal antibody;
PD-1 = programmed death receptor-1; **PD-L1** = programmed death ligand-1.
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A 23-year-old woman comes to the emergency department with vaginal bleeding and lower abdominal cramps. Her last menstrual period was 6 weeks ago, and a home pregnancy test was positive. She has no medical history and does not use tobacco or alcohol. Pelvic ultrasonography reveals a gestational sac in the left fallopian tube without evidence of rupture. A single dose of methotrexate is administered to treat her condition. Which of the following substances will most likely accumulate in embryonic tissues as a result of treatment?

A. Dihydrofolate polyglutamate

B. Folinic acid

C. Para-aminobenzoic acid

D. Tetrahydrofolate

E. Thymidylic acid

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- ✓ A. Dihydrofolate polyglutamate (50%)
- B. Folinic acid (6%)
- C. Para-aminobenzoic acid (8%)
- D. Tetrahydrofolate (29%)
- E. Thymidylic acid (5%)

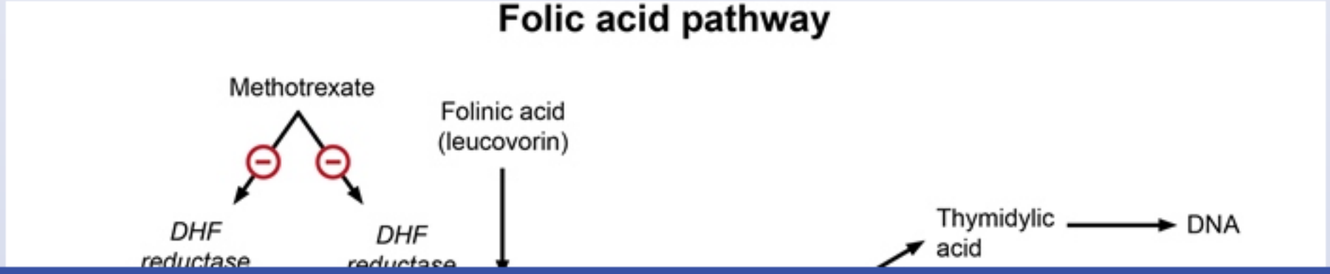
Omitted
Correct answer
A

50%
Answered correctly

02 secs
Time Spent

02/24/2020
Last Updated

Explanation



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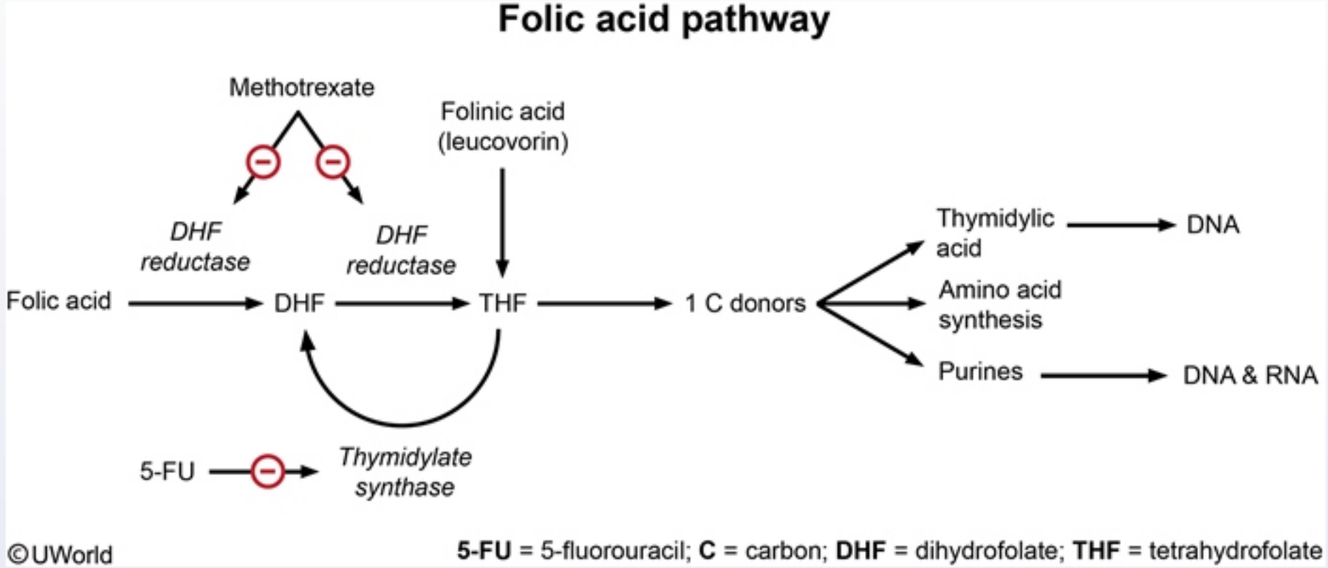

Methotrexate (MTX), a **folate antagonist**, is the drug of choice for non-surgical treatment of an early, unruptured ectopic pregnancy. Folic acid is a required precursor to nucleic acid synthesis. Barriers to its metabolism are especially effective in hindering the growth of rapidly proliferating cells such as in a developing embryo or certain types of cancer.

Normally, folic acid is reduced to dihydrofolate (DHF) by dihydrofolate reductase and then reduced further to **tetrahydrofolate** (THF), an integral precursor of **DNA synthesis**. MTX is structurally similar to folic acid and competitively and irreversibly **inhibits DHF reductase**. DHF reductase inhibition prevents the formation of THF **(Choice D)**.

After entering the target cell, MTX undergoes **polyglutamation**, which prevents the movement of MTX out of the cell, resulting in intracellular accumulation of MTX for later use. Similarly, folate and recycled DHF are stored within the cell via polyglutamation. Because MTX inhibits DHF reductase, folic acid and DHF polyglutamate will accumulate in cells.

(Choice B) Folinic acid (leucovorin) is a reduced form of folic acid that can be used to counter the toxic effects of MTX chemotherapy. Folinic acid selectively "rescues" normal cells by competing with MTX for DHF reductase binding sites. It can reactivate DHF reductase, therefore allowing re-initiation of DNA synthesis.

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(Choice C) Para-aminobenzoic acid (PABA) is a folic acid precursor in prokaryotes. Sulfonamide antibiotics are chemical analogues of PABA that inhibit the enzyme dihydropteroate synthetase, preventing bacterial conversion of PABA to folic acid. Humans lack the ability to convert PABA to folic acid and require dietary folate.

(Choice E) Thymidylic acid is a nucleotide that contributes to pyrimidine formation. Its synthesis is inhibited by MTX.

Educational objective:
Methotrexate is a folic acid antagonist used to treat ectopic pregnancy. It competitively inhibits the enzyme dihydrofolate (DHF) reductase, which catalyzes the synthesis of tetrahydrofolate. DHF reductase inhibition causes the intermediate DHF to accumulate intracellularly.

References

- Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy.
- Low-dose methotrexate results in the selective accumulation of aminoimidazole carboxamide ribotide in an erythroblastoid cell line.

Pharmacology Hematology & Oncology Methotrexate

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A 51-year-old woman comes to the office for a follow-up visit. Three weeks ago, she had a screening mammogram that was suspicious for malignancy. An ultrasound-guided needle aspiration was performed and showed invasive ductal carcinoma. The patient underwent a lumpectomy with axillary dissection and was found to have no metastatic disease. Immunohistochemical analysis of the tumor specimen was significant for the following:

Estrogen receptor	Positive
Progesterone receptor	Positive
Human epidermal growth factor receptor 2	Positive

Adjuvant therapy with a monoclonal antibody is started. Which of the following is the most likely target of this drug?

A. Estrogen receptor
B. Peripheral aromatase enzyme
C. Receptor activator of nuclear factor kappa-B ligand
D. Tyrosine kinase receptor
E. Vascular endothelial growth factor

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Estrogen receptor	Positive
Progesterone receptor	Positive
Human epidermal growth factor receptor 2	Positive

Adjuvant therapy with a monoclonal antibody is started. Which of the following is the most likely target of this drug?

A. Estrogen receptor (30%)
B. Peripheral aromatase enzyme (4%)
C. Receptor activator of nuclear factor kappa-B ligand (8%)
✓ D. Tyrosine kinase receptor (48%)
E. Vascular endothelial growth factor (7%)

Omitted
Correct answer
D

48%
Answered correctly

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Time Spent

04/08/2020
Last Updated

Explanation

Explanation

This patient has localized invasive ductal **breast carcinoma** that shows estrogen receptor (ER), progesterone receptor (PR), and **human epidermal growth factor receptor 2 (HER2)** positivity. **Trastuzumab** is a monoclonal antibody used in the management of patients with HER2-positive breast cancer. It binds to a portion of the extracellular domain of HER2 and prevents activation of a transmembrane **tyrosine kinase**. This downregulates cellular proliferation and promotes apoptosis. Approximately 20% of all invasive breast cancers overexpress HER2; this can also be found in other solid tumors (eg, stomach, lung, ovary).

(Choices A and B) Hormone receptor-positive breast cancer (ER and/or PR overexpression) is treated with antiestrogen medications to reduce tumor cell proliferation. Premenopausal patients are typically treated with selective estrogen receptor modulators (eg, tamoxifen), while aromatase inhibitors (eg, anastrozole, letrozole) are used in postmenopausal women. However, these medications are not monoclonal antibodies.

(Choice C) Receptor activator of nuclear factor kappa-B ligand (RANKL) activates osteoclasts; RANKL expression on bone may contribute to bone metastases by binding to RANK on tumor cells. Denosumab, a human monoclonal antibody against RANKL, is used to reduce skeletal-related events if metastasis to bone occurs.

(Choice E) Vascular endothelial growth factor (VEGF), which also binds to a tyrosine kinase receptor, induces angiogenesis. VEGF inhibitors, such as the monoclonal antibody bevacizumab, have a role in treatment of some metastatic cancers (eg, colon, lung).

Educational objective:
Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor that is overexpressed in 20% of breast cancer patients. In such patients, HER2 blockade with the monoclonal antibody trastuzumab downregulates cellular proliferation and promotes apoptosis.

References

- Trastuzumab--mechanism of action and use in clinical practice.
- HER2: biology, detection, and clinical implications.

Pharmacology	Hematology & Oncology	Trastuzumab
Subject	System	Topic

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A 78-year-old man is found unresponsive and is brought by ambulance to the emergency department. Upon arrival, the family says he has a complicated medical history and takes multiple medications but has no known drug allergies. Noncontrast CT scan of the head reveals intracranial hemorrhage. The patient is given a recombinant biologic agent that has antigen homology with factor Xa but no catalytic effect. The agent is most likely to antagonize the effects of which of the following drugs?

A. Apixaban
B. Aspirin
C. Dabigatran
D. Ticagrelor
E. Warfarin

Submit

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- ✓ A. Apixaban (83%)
- B. Aspirin (0%)
- C. Dabigatran (10%)
- D. Ticagrelor (1%)
- E. Warfarin (3%)

Omitted
Correct answer
A

83%
Answered correctly

02 secs
Time Spent

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Last Updated

Explanation

Anticoagulation reversal for life-threatening bleeding		
Drug	**Mechanism of action**	**Reversal**
Warfarin	• ↓ Production of vitamin K–dependent clotting factors	• PCC • Intravenous vitamin K

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Drug	**Mechanism of action**	**Reversal**
Warfarin	• ↓ Production of vitamin K–dependent clotting factors	• PCC • Intravenous vitamin K
Dabigatran	• Direct inhibition of clot-bound and free thrombin	• Idarucizumab (mAb fragment that binds dabigatran) • PCC
Factor Xa inhibitors (eg, rivaroxaban, apixaban)	• Direct inhibition of factor Xa	• Recombinant modified factor Xa (eg, andexanet) • PCC
Heparin	• ↑ Activity of antithrombin III	• Protamine sulfate

mAb = monoclonal antibody; **PCC** = prothrombin complex concentrate (contains vitamin K–dependent clotting factors).

This patient's intracranial hemorrhage was likely treated with **andexanet alfa**, a biologic agent that shares homology with factor Xa but has no proteolytic effect. It is administered to patients who have **life-threatening bleeding** while on a factor Xa inhibitor (eg, rivaroxaban, **apixaban**). The similarity of andexanet to factor Xa allows it to function as a **decoy** that binds to factor Xa inhibitors. This restores intravascular coagulation by increasing the availability of endogenous factor Xa, which converts prothrombin to thrombin and generates fibrin clots. Andexanet is reserved for life-threatening bleeding because it is associated with a significant risk of thrombosis.

(Choice B) Aspirin inhibits cyclooxygenase, which prevents platelet aggregation by blocking the generation of thromboxane A2. There is no reversal agent for aspirin widely available. Aspirin does not target factor Xa.

(Choice C) Dabigatran is a direct oral anticoagulant (DOAC) that inhibits circulating and clot-bound thrombin. It is reversed by idarucizumab, a

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(Choice C) Dabigatran is a direct oral anticoagulant (DOAC) that inhibits circulating and clot-bound thrombin. It is reversed by idarucizumab, a monoclonal antibody fragment that binds to and inhibits dabigatran. Although dabigatran is a DOAC, it targets thrombin rather than factor Xa.

(Choice D) Ticagrelor blocks the $P2Y_{12}$ adenosine diphosphate receptor on the surface of platelets, which prevents platelet aggregation. Its activity is not mediated by factor Xa.

(Choice E) Warfarin is a vitamin-K antagonist that prevents the generation of vitamin–K dependent clotting factors by blocking epoxide reductase in the liver. It is reversed by the administration of vitamin K.

Educational objective:
Andexanet alfa is a factor Xa decoy that has no proteolytic effect. It is administered to patients on factor Xa inhibitors (eg, rivaroxaban, apixaban) who have life-threatening bleeding in order to reverse the anticoagulation effect.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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Two antineoplastic drugs are shown to inhibit intracellular thymidylate formation. The chemotherapeutic effect of drug X can be overcome by N^5-formyl-tetrahydrofolate supplementation, but that of drug Y is not affected. The drugs described in this scenario are most likely which of the following?

	Drug X	Drug Y
A.	Cytarabine	Gemcitabine
B.	Fluorouracil	Leucovorin
C.	Fludarabine	Methotrexate
D.	Methotrexate	Fluorouracil
E.	Gemcitabine	Fludarabine

Submit

Two antineoplastic drugs are shown to inhibit intracellular thymidylate formation. The chemotherapeutic effect of drug X can be overcome by N^5-formyl-tetrahydrofolate supplementation, but that of drug Y is not affected. The drugs described in this scenario are most likely which of the following?

	Drug X	Drug Y
A. (1%)	Cytarabine	Gemcitabine
B. (7%)	Fluorouracil	Leucovorin
C. (4%)	Fludarabine	Methotrexate
✓ D. (85%)	Methotrexate	Fluorouracil
E. (0%)	Gemcitabine	Fludarabine

Omitted
Correct answer
D

85%
Answered correctly

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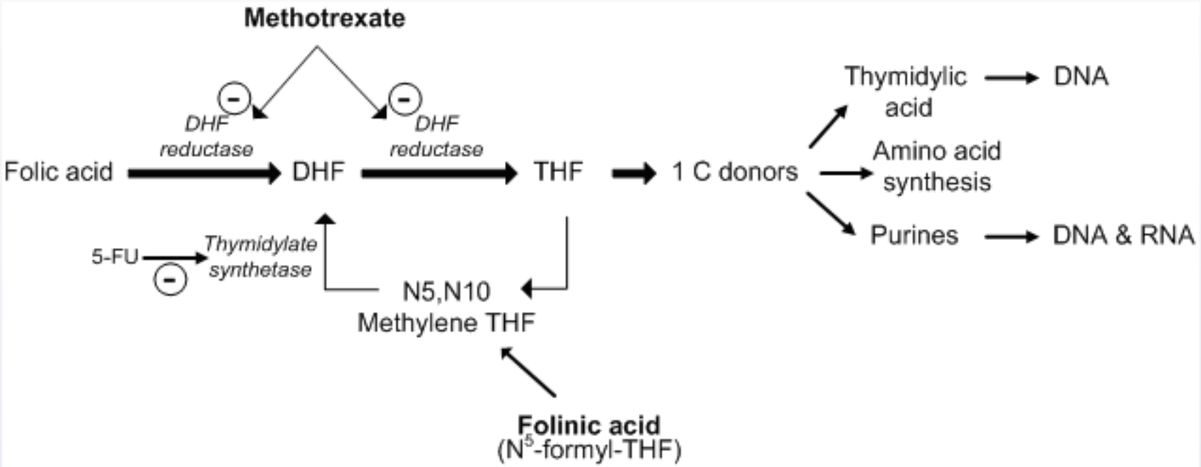
02/03/2020
Last Updated

Explanation

Methotrexate

Explanation



The two antineoplastic agents described in the question stem are methotrexate (Drug X) and 5-fluorouracil (Drug Y). Methotrexate is a folic acid analog that functions by binding and inactivating dihydrofolate reductase, the enzyme responsible for reducing folic acid to tetrahydrofolate. Tetrahydrofolate participates in the transfer of carbon groups in certain intracellular reactions including purine and thymidine synthesis. 5-fluorouracil (5-FU) is a pyrimidine analog that primarily functions to inhibit DNA synthesis by inhibition of thymidylate synthetase after enzymatic conversion to its nucleotide floxuridine monophosphate by any of a number of intracellular reactions.

The key metabolic difference between methotrexate and 5-fluorouracil is that methotrexate prevents the reduction of folic acid to tetrahydrofolate, while 5-FU binds tetrahydrofolate and thymidylate synthetase in a stable-reaction intermediate form, thereby effectively decreasing the amount of thymidylate synthetase available for thymidine synthesis.

Leucovorin (N^5-formyl-tetrahydrofolate) is a tetrahydrofolate derivative that does not require reduction by dihydrofolate reductase before it can function as a cofactor for thymidylate synthase and other enzymes involved with purine and amino acid synthesis. Because leucovorin bypasses the dihydrofolate reductase step that is inhibited by methotrexate, it can be used to "rescue" normal cells from the toxicity of methotrexate. 5-FU, on the other hand, requires the presence of reduced folate in order to form complexes with thymidylate synthetase. 5-FU has a reduced cytotoxic effect in cells that are deficient in tetrahydrofolate. For this reason, leucovorin can be utilized to potentiate the toxicity of fluoropyrimidines such as fluorouracil by strengthening the association of the drug with thymidylate synthase.

(N^5-formyl-THF)

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(Choice A) Cytarabine, like 5-FU, is also a pyrimidine analog antimetabolite that is incorporated into DNA leading to strand termination. It does not affect folate metabolism. Gemcitabine is another pyrimidine analog that functions much like cytarabine. It differs from cytarabine in that it is not S-phase specific, likely owing to additional cytotoxic functions such as inhibition of ribonucleotide reductase.

(Choice C) Fludarabine is a deamination-resistant purine nucleotide analog that exerts its cytotoxicity by many mechanisms, including inhibition of DNA polymerase, DNA primase, DNA ligase, and ribonucleotide reductase. Fludarabine is used to treat chronic lymphocytic leukemia (CLL).

Educational Objective:
Methotrexate and 5-FU both effectively inhibit thymidylate formation, but the chemotherapeutic effect of methotrexate is overcome by N^5-formyl-tetrahydrofolate (folinic acid, leucovorin) supplementation.

Pharmacology Hematology & Oncology Chemotherapy

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Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 62-year-old woman is being evaluated for worsening anemia. The patient was admitted to the hospital 2 days ago due to acute pyelonephritis. She has been treated with intravenous ceftriaxone, and her fever and urinary symptoms have gradually improved. The patient has no history of anemia and has had no symptoms of urinary or gastrointestinal bleeding. Laboratory results are as follows:

	On admission	2 days later
Hemoglobin	12.3 g/dL	8.4 g/dL
Platelets	285,000/mm^3	300,000/mm^3
Leukocytes	14,800/mm^3	10,000/mm^3
Serum creatinine	1.0 mg/dL	0.8 mg/dL
Serum bilirubin	0.8 mg/dL	2.4 mg/dL
Prothrombin time	12 sec	11 sec

Her antibiotics are changed to a different medication class, and the patient is discharged a few days later. At a follow-up office visit 2 weeks later, her laboratory abnormalities have resolved. Which of the following is the most likely cause of this patient's anemia?

A. Antibody-mediated erythrocyte injury
B. Cytokine-mediated iron dysregulation
C. Drug-induced myelosuppression
D. Erythrocyte enzyme deficiency
E. Microthrombi-induced erythrocyte injury

Submit

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Prothrombin time	12 sec	11 sec

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- A. Antibody-mediated erythrocyte injury (58%)
- B. Cytokine-mediated iron dysregulation (4%)
- C. Drug-induced myelosuppression (6%)
- D. Erythrocyte enzyme deficiency (24%)
- E. Microthrombi-induced erythrocyte injury (5%)

Omitted
Correct answer

58%
Answered correctly

02 secs
Time Spent

05/19/2020
Last Updated

Drug-induced immune-mediated hemolytic anemia	
Pathogenesis	• Drug coats erythrocytes → IgG binding → splenic destruction of RBCs (extravascular hemolysis) • Drug triggers immune complexes → complement-mediated destruction of RBCs (intravascular hemolysis)

Manifestations	• Sudden onset (within hours of exposure)
	• Anemia: fatigue, pallor, dyspnea
	• Hemolysis: jaundice, dark urine, abdomen/back pain
	  ∘ ↑ Reticulocytes, indirect bilirubin & LDH
	  ∘ ↓ Haptoglobin
	  ∘ Spherocytes on peripheral blood smear
	  ∘ + Direct Coombs test (anti-IgG, anti-C3)

Treatment	• Discontinue offending drug
LDH = lactate dehydrogenase; **RBC** = red blood cell.	

This patient developed anemia and hyperbilirubinemia during treatment with ceftriaxone, raising strong suspicion for **drug-induced hemolytic anemia**. The most common triggers of drug-induced hemolysis are anti-inflammatory medications, penicillins, and cephalosporins (eg, **ceftriaxone**). Although the mechanism of erythrocyte injury (eg, oxidative, complement mediated) varies depending on the medication, penicillins and cephalosporins typically cause hemolysis by binding to the erythrocyte surface, which creates a **hapten for IgG attachment**. Antibody-coated erythrocytes are then partially or wholly phagocytized by splenic macrophages, leading to **extravascular hemolysis**.

Hemolysis is often associated with symptomatic anemia (eg, fatigue, pallor) and signs of hyperbilirubinemia (eg, jaundice, dark urine). Laboratory

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Hemolysis is often associated with symptomatic anemia (eg, fatigue, pallor) and signs of hyperbilirubinemia (eg, jaundice, dark urine). Laboratory evaluation will typically reveal **elevated indirect bilirubin** (heme breakdown product), elevated lactate dehydrogenase (intracellular enzyme), reticulocytosis (increased immature RBCs), and lowered haptoglobin (binds free hemoglobin). The diagnosis is confirmed with the **direct antiglobulin (Coombs) test**, which detects IgG or C3 (a complement fragment) on the erythrocyte surface. Because hemolysis is triggered by the direct binding of the penicillin or cephalosporin to the erythrocyte membrane, **cessation of the offending drug** eliminates the antibody target and generally leads to complete resolution of symptoms within days.

(Choice B) Anemia of chronic disease is caused by cytokine-mediated iron dysregulation. Although chronic infection (eg, viral hepatitis, tuberculosis) is a common trigger, anemia of chronic disease is gradual in onset and is not associated with hyperbilirubinemia (no RBC lysis).

(Choice C) Certain antibiotics (eg, sulfa medications, chloramphenicol) are associated with myelosuppression. However, these medications generally cause pancytopenia, not isolated anemia; in addition, hyperbilirubinemia is not seen.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency is marked by hemolysis in the setting of oxidative stress due to infection, oxidizing medication, or oxidative foods. Although this patient has an infection, ceftriaxone is not an oxidizing medication. In addition, G6PD deficiency is X-linked; therefore, symptoms are less common in women.

(Choice E) Severe infections can trigger disseminated intravascular coagulation, a consumptive coagulopathy associated with anemia due to erythrocyte injury from microvascular thrombi. However, these patients have prolonged coagulation times and thrombocytopenia.

Educational objective:
Penicillins and cephalosporins are common triggers for drug-induced hemolytic anemia because they can bind to the erythrocyte surface and act as haptens for IgG attachment. Subsequent clearance of IgG-coated erythrocytes by splenic macrophages leads to hemolytic anemia. Withdrawal of the offending drug usually leads to complete resolution of symptoms.

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Pharmacology	Hematology & Oncology	Hemolytic anemia
Subject	System	Topic

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A 57-year-old female presents to the emergency department after vomiting a substance that resembled "coffee grounds." She reports that she now feels lightheaded as well. Her past medical history is significant for deep venous thromboses, for which she takes warfarin, and occasional joint pain, for which she takes aspirin. Her blood pressure is 90/60 mm Hg and her pulse is 110 beats per minute. Which of the following substances would provide the fastest reversal of warfarin's effects?

A. Vitamin K
B. Protamine
C. Aminocaproic acid
D. Fresh frozen plasma
E. Cryoprecipitate
F. Desmopressin

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- A. Vitamin K (16%)
- B. Protamine (2%)
- C. Aminocaproic acid (1%)
- ✓ D. Fresh frozen plasma (78%)
- E. Cryoprecipitate (1%)
- F. Desmopressin (0%)

Omitted
Correct answer
D

78%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Warfarin is the most commonly used agent for long-term anticoagulation in the setting of venous thromboses and pulmonary thromboembolism. Warfarin inhibits the vitamin K dependent γ-carboxylation of the glutamic acid residues of clotting factors II, VII, IX and X, causing production of dysfunctional coagulation proteins.

The therapeutic effect of warfarin is monitored by measuring the prothrombin time (PT). The international normalized ratio (INR) is a standardized

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The therapeutic effect of warfarin is monitored by measuring the prothrombin time (PT). The international normalized ratio (INR) is a standardized PT. The target INR for therapeutic warfarin anticoagulation is 2-3. Bleeding is a common complication of warfarin therapy and the risk is increased with INRs above 3.0. Treatment of life-threatening bleeding requires rapid reversal using fresh frozen plasma. Vitamin K can help to reverse warfarin action, but the effects take time.

(Choice B) Protamine is used for heparin reversal. It acts by binding and chemically inactivating heparin.

(Choice C) Aminocaproic acid is an antifibrinolytic agent that inhibits plasminogen activators and, to a lesser degree, antiplasmin activity. Aminocaproic acid helps achieve hemostasis when fibrinolysis is the cause of bleeding.

(Choice E) Whereas fresh frozen plasma contains all of the coagulation factors, cryoprecipitate contains only cold-soluble proteins (Factor VIII, fibrinogen, von Willebrand factor, and vitronectin).

(Choice F) Desmopressin is a synthetic analogue of anti-diuretic hormone (ADH) used in the treatment of diabetes insipidus. At high doses, desmopressin increases factor VIII activity in patients with hemophilia A and von Willebrand disease. High-dose desmopressin can help control bleeding associated with these disorders.

Educational Objective:
Both vitamin K and fresh frozen plasma are used for reversing warfarin-induced anticoagulation. Fresh frozen plasma rapidly reverses warfarin's effects whereas vitamin K requires time for clotting factor re-synthesis.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 61-year-old man comes to the hospital due to 2 days of right leg swelling. He recently flew back to the United States from Japan, where he was visiting his daughter who is spending a semester abroad. The patient has a medical history of hypertension and hyperlipidemia. Temperature is 37.2 C (99 F), blood pressure is 136/70 mm Hg, and pulse is 90/min. Pulse oximetry shows 99% on room air. Cardiopulmonary examination is within normal limits. There is tenderness and swelling of the right lower extremity up to the mid thigh. Laboratory studies, including prothrombin time and activated partial thromboplastin time, are normal. Venous doppler reveals an occluding thrombus in the right femoral and popliteal veins. The patient is started on rivaroxaban. This drug inhibits which of the following?

A. Factor VIII

B. Factor Xa

C. Glycoprotein IIb/IIIa

D. Platelet P2Y12

E. Thrombin

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A. Factor VIII (0%)
✓ B. Factor Xa (87%)
C. Glycoprotein IIb/IIIa (3%)
D. Platelet P2Y12 (1%)
E. Thrombin (6%)

Omitted
Correct answer
B

87%
Answered correctly

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04/05/2020
Last Updated

Explanation

Anticoagulants & their mechanism of action

Intrinsic pathway

Extrinsic pathway

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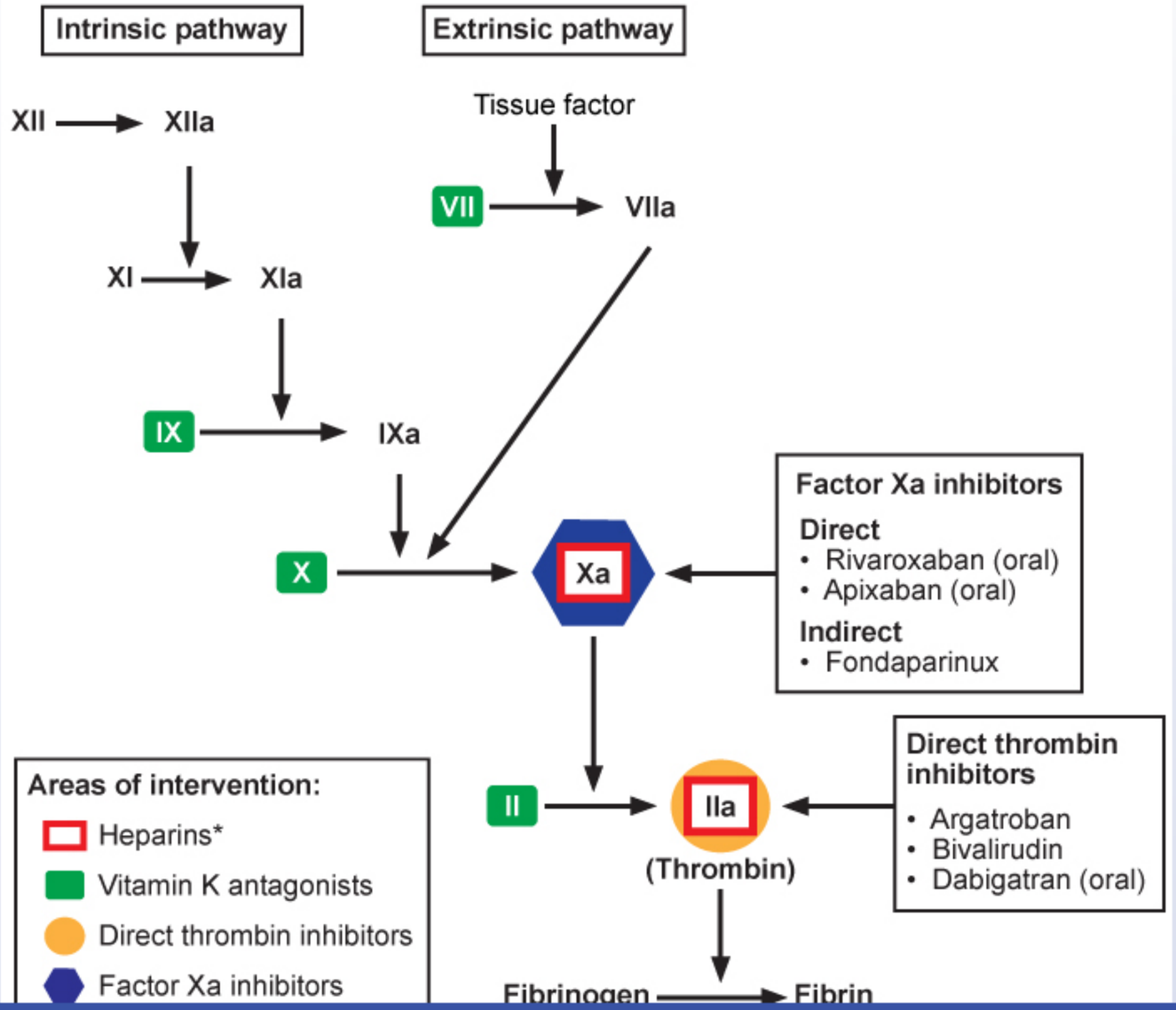
Anticoagulants & their mechanism of action



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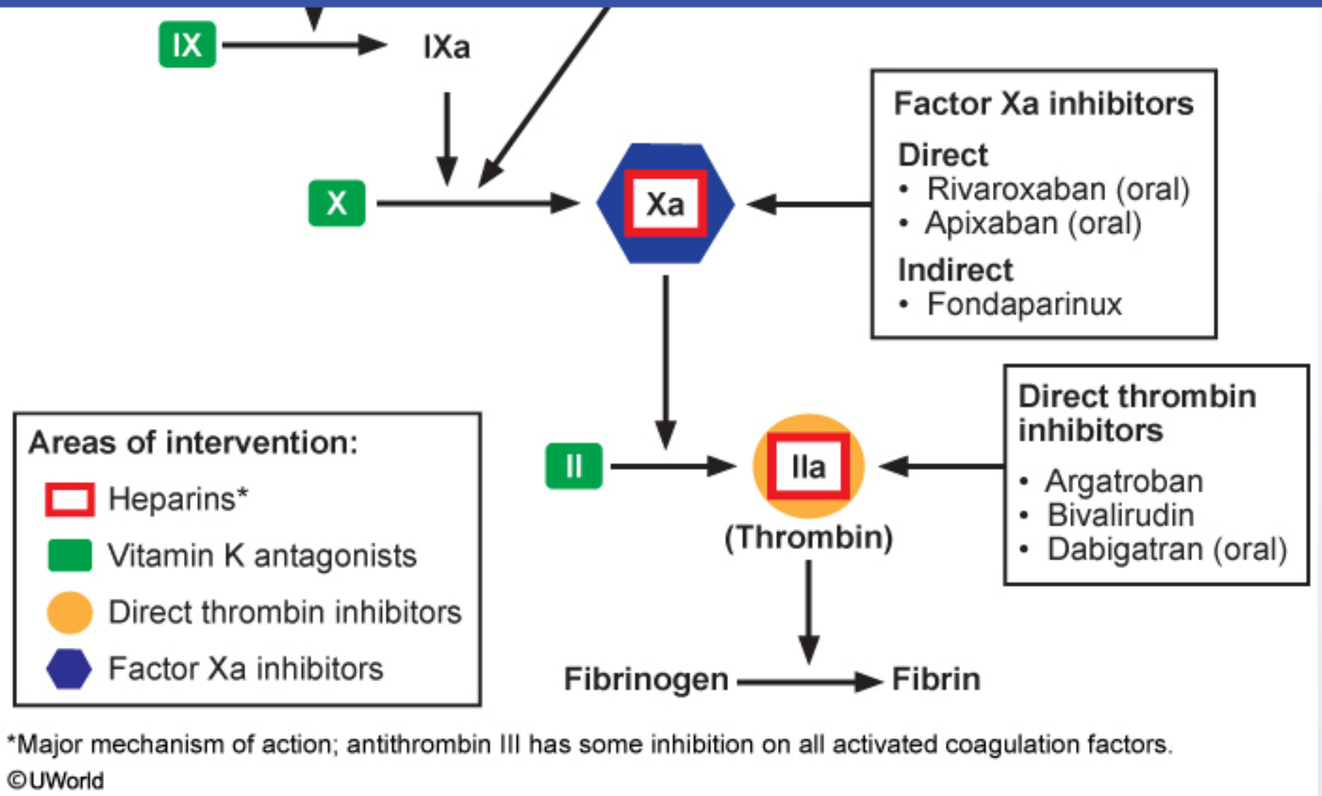

*Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
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This patient has right lower extremity proximal deep venous thrombosis (DVT), with his recent long flight from Japan being a possible risk factor. Many patients with DVT receive long-term anticoagulation with warfarin. Alternates include direct **factor Xa** inhibitors (eg, rivaro**Xa**ban, api**Xa**ban), which bind to the active site of factor Xa and prevent thrombin formation. These drugs can be administered orally as monotherapy and do not require laboratory monitoring. They are used for venous thromboembolism treatment as well as for stroke prophylaxis in patients with atrial fibrillation (who are at risk for embolic stroke).

(Choice A) Factor VIII replacement (not inhibition) is the mainstay of hemophilia A treatment.

(Choice C) Eptifibatide inhibits platelet aggregation and thrombosis by blocking the glycoprotein IIb/IIIa receptor, which is the binding site for fibrinogen. This drug is typically used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

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Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
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This patient has right lower extremity proximal deep venous thrombosis (DVT), with his recent long flight from Japan being a possible risk factor. Many patients with DVT receive long-term anticoagulation with warfarin. Alternates include direct **factor Xa** inhibitors (eg, rivaro**Xa**ban, api**Xa**ban), which bind to the active site of factor Xa and prevent thrombin formation. These drugs can be administered orally as monotherapy and do not require laboratory monitoring. They are used for venous thromboembolism treatment as well as for stroke prophylaxis in patients with atrial fibrillation (who are at risk for embolic stroke).

(Choice A) Factor VIII replacement (not inhibition) is the mainstay of hemophilia A treatment.

(Choice C) Eptifibatide inhibits platelet aggregation and thrombosis by blocking the glycoprotein IIb/IIIa receptor, which is the binding site for fibrinogen. This drug is typically used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

(Choice D) Ticagrelor binds the adenosine diphosphate (ADP) P2Y12 receptor on platelets, which prevents platelet aggregation by blocking ADP-mediated activation of the glycoprotein IIb/IIIa receptor complex. This drug is also used in acute coronary syndrome and in patients undergoing percutaneous coronary intervention.

(Choice E) Dabigatran is an oral direct thrombin inhibitor that inactivates both circulating and clot-associated thrombin. It is also used for treatment of thromboembolic disease and stroke prophylaxis in atrial fibrillation.

Educational objective:
Rivaroxaban is an oral anticoagulant that directly inhibits factor Xa. It is used in venous thromboembolism and atrial fibrillation.

References

- New oral anticoagulants: their advantages and disadvantages compared with vitamin K antagonists in the prevention and treatment of patients with thromboembolic events.

Pharmacology	Hematology & Oncology	Venous thromboembolism
Subject	System	Topic

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A 64-year-old woman is hospitalized for elective hip replacement surgery. She has osteoarthritis and is experiencing progressive right hip pain that limits her daily activities. The patient also has a history of hypertension and hypothyroidism. Her blood pressure is 130/80 mm Hg and pulse is 90/min. BMI is 31.5 kg/m^2. Her serum creatinine is 0.9 mg/dL. She undergoes surgery without complications and is postoperatively started on a medication that is a low molecular weight fraction of a negatively charged chemical stored in mast cell granules. Which of the following is the most likely mechanism of action of the medication used?

A. Binds antithrombin III

B. Binds to the thrombin active site

C. Blocks ADP receptors

D. Combines with proactivator plasminogen

E. Inhibits arachidonate product formation

Submit

A 64-year-old woman is hospitalized for elective hip replacement surgery. She has osteoarthritis and is experiencing progressive right hip pain that limits her daily activities. The patient also has a history of hypertension and hypothyroidism. Her blood pressure is 130/80 mm Hg and pulse is 90/min. BMI is 31.5 kg/m^2. Her serum creatinine is 0.9 mg/dL. She undergoes surgery without complications and is postoperatively started on a medication that is a low molecular weight fraction of a negatively charged chemical stored in mast cell granules. Which of the following is the most likely mechanism of action of the medication used?

- ✓ A. Binds antithrombin III (78%)
- B. Binds to the thrombin active site (13%)
- C. Blocks ADP receptors (3%)
- D. Combines with proactivator plasminogen (2%)
- E. Inhibits arachidonate product formation (2%)

Omitted
Correct answer
A

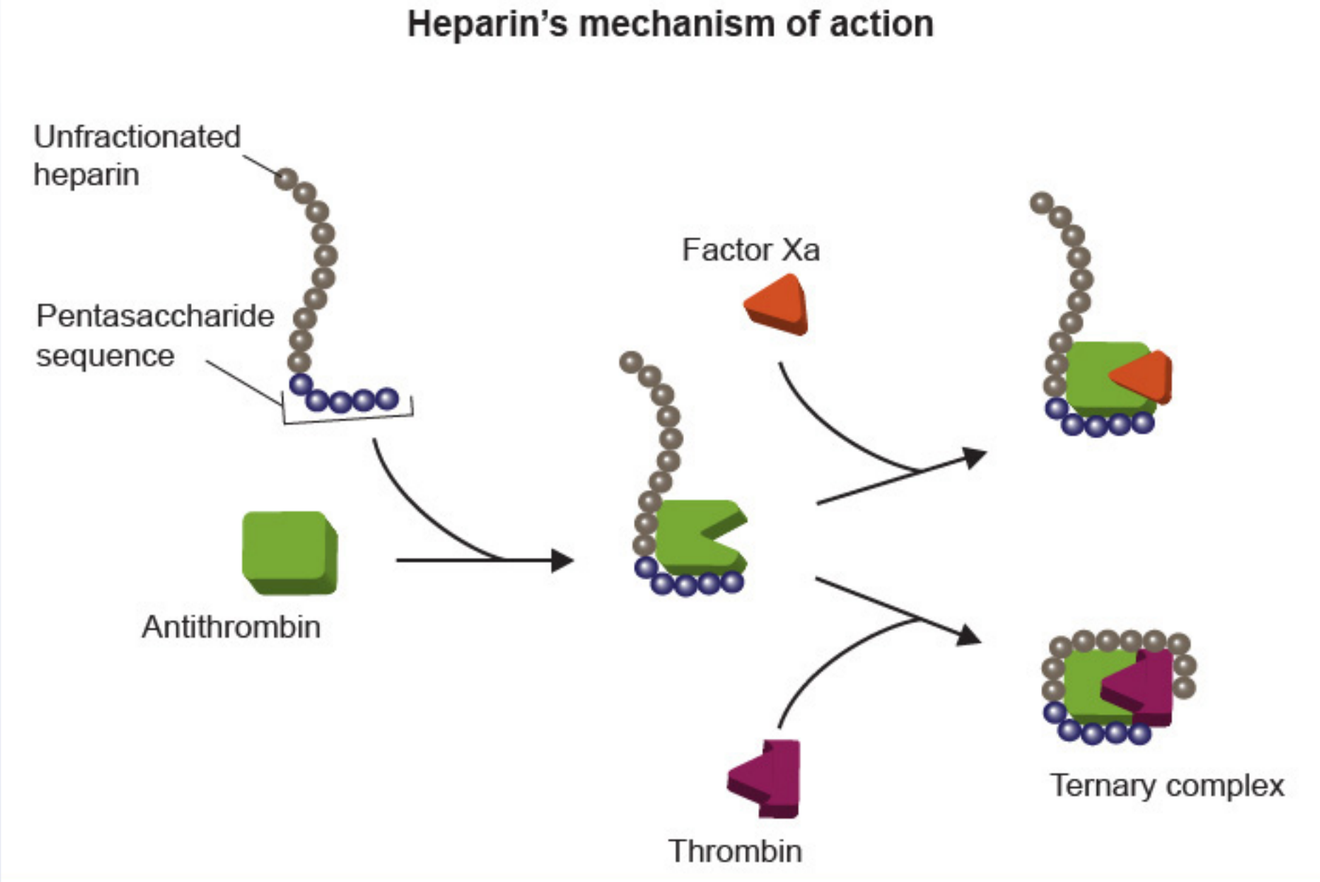
78%
Answered correctly

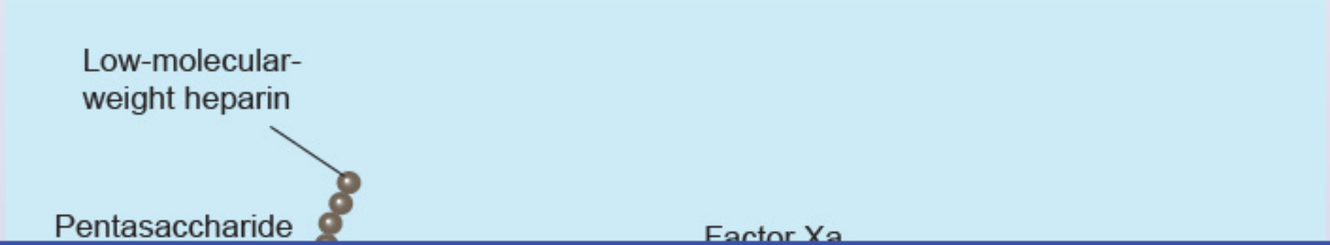
02 secs
Time Spent

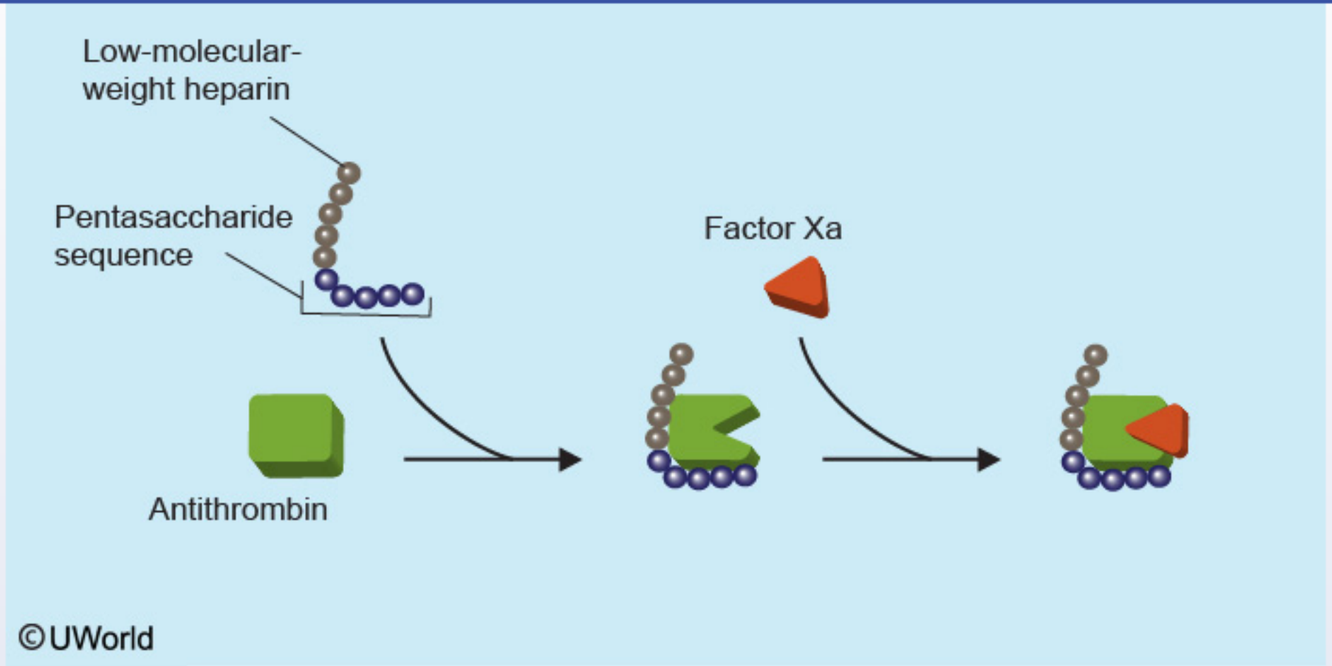
06/30/2020
Last Updated

Explanation

Explanation







Nonambulatory hospitalized patients are at increased risk for developing lower extremity **deep venous thrombosis** (DVT), which can lead to pulmonary embolism. In patients undergoing elective surgery without **prophylaxis** against DVT, the risk can be even higher, particularly with certain orthopedic procedures such as hip and knee replacement. In such cases, DVT prophylaxis is usually initiated within hours of wound closure.

Unfractionated and low molecular weight **heparins** (LMWHs) are commonly used for DVT prevention in inpatient settings. Administration of heparin (a negatively charged chemical naturally present in mast cells) increases the effect of the naturally occurring anticoagulant **antithrombin III (AT III)**. Unfractionated heparin binds to AT III via a pentasaccharide in the heparin chain. This results in a conformational change of AT III, which subsequently inhibits factor Xa and neutralizes thrombin, promoting anticoagulation. AT III activated by **LMWH** (which has better bioavailability and does not need laboratory monitoring when given therapeutically) acts predominantly on **factor Xa**, not thrombin.

(Choice B) Direct thrombin inhibitors directly inhibit thrombin-mediated fibrin formation. Lepirudin and argatroban (parenteral) are primarily used for management of heparin-induced thrombocytopenia. Dabigatran (oral) is used for DVT prevention and treatment and for stroke prevention in

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(Choice C) Clopidogrel and ticlopidine inhibit ADP-mediated platelet aggregation. They are useful following percutaneous coronary intervention and for treatment of unstable angina and non-ST segment elevation myocardial infarction.

(Choice D) Use of drugs that convert inactive plasminogen to plasmin leads to fibrinolysis and clot lysis; such medications are given for clot lysis in acute myocardial infarction, pulmonary embolism, and arterial thrombosis.

(Choice E) Aspirin irreversibly acetylates platelet cyclooxygenase-I, leading to decreased formation of thromboxane A2. Aspirin is used for primary and secondary prevention of myocardial infarction and stroke.

Educational objective:
Heparin is commonly used for the prevention of deep venous thrombosis in nonambulatory patients or those undergoing elective surgery, especially hip and knee surgery. Heparin increases the effect of the naturally occurring anticoagulant antithrombin III.

References

- New Antithrombotic Drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Page(s): PMC3278067

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References

- New Antithrombotic Drugs: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Page(s): PMC3278067
- New anticoagulants.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 5-year-old boy is brought to the emergency department due to an hour of epistaxis after he was elbowed in the face during a basketball game. He has a history of prolonged bleeding from the gums after brushing his teeth. Vital signs are normal. The patient has scattered bruises along his arms and legs. He receives desmopressin, which stops the bleeding. This treatment most likely improved the patient's condition through which of the following therapeutic mechanisms?

A. Binds to antidiuretic hormone receptors

B. Increases circulating factor IX

C. Increases circulating von Willebrand factor

D. Increases platelet count

E. Increases vitamin K–dependent coagulation factors

F. Relaxes vascular smooth muscle cells

Submit

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- A. Binds to antidiuretic hormone receptors (6%)
- B. Increases circulating factor IX (2%)
- ✓ C. Increases circulating von Willebrand factor (84%)
- D. Increases platelet count (1%)
- E. Increases vitamin K–dependent coagulation factors (2%)
- F. Relaxes vascular smooth muscle cells (1%)

Omitted
Correct answer
C

84%
Answered correctly

02 secs
Time Spent

06/05/2020
Last Updated

Explanation

Effects of desmopressin (DDAVP) therapy	
Mild hemophilia A & **Type 1 von Willebrand disease**	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding

Effects of desmopressin (DDAVP) therapy	
Mild hemophilia A & **Type 1 von Willebrand disease**	Increases circulating factor VIII & endothelial secretion of vWF to stop bleeding
Central diabetes insipidus & **Nocturnal enuresis**	Binds to V2 receptors in renal tubular cells, leading to increased aquaporin channels, increased water reabsorption & decreased urine output

vWF = von Willebrand factor.

This patient's history of prolonged mucosal bleeding (eg, oropharyngeal, nasal), easy bruising, and responsiveness to desmopressin (DDAVP) likely indicate **von Willebrand disease** (vWD), the most common inherited bleeding disorder. VWD is caused by qualitative or quantitative defect in von Willebrand factor (vWF), a multimeric glycoprotein synthesized by endothelial cells and platelets. VWF contributes to hemostasis by forming a bridge between platelets and exposed subendothelial components at sites of injury and by serving as a carrier protein for factor VIII (whose half-life is tremendously shortened when not bound to vWF).

Treatment of minor bleeding episodes in patients with vWD often involves **desmopressin** (DDAVP), a synthetic analogue of antidiuretic hormone that does not induce vasoconstriction. DDAVP induces a rapid and transient **increase in vWF** and factor VIII by indirectly releasing these compounds from **endothelial storage sites**. DDAVP is most useful in the acute setting, as repeated doses have limited effectiveness due to tachyphylaxis (endothelial stores become depleted).

(Choices A and F) Antidiuretic hormone binds to the vasopressin 2 receptor on renal tubular cells, which leads to increased aquaporin channels, increased water reabsorption, and decreased urine output. It also binds to the vasopressin 1 (V1) receptor on vascular smooth muscle, which results in vasoconstriction. In contrast, DDAVP has antidiuretic effects but little or no vasoactive (vasoconstrictive) effects because it only binds to the V2 receptor.

(Choice B) Factor IX, a vitamin K–dependent clotting factor produced in the liver, is deficient in hemophilia B. DDAVP has no effect on factor IX levels. Hemophilia B must be treated with factor IX replacement.

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(Choice D) Platelets form the initial hemostatic plug when bleeding occurs. DDAVP has no effect on platelet number.

(Choice E) Patients with vitamin K deficiency are prone to bleeding due to decreased vitamin K–dependent coagulation factors (factors II, VII, IX, and X). Vitamin K deficiency is typically seen in patients with fat malabsorption (eg, pancreatic insufficiency) or those on warfarin, a vitamin K antagonist.

Educational objective:
Patients with symptomatic von Willebrand disease can be treated with desmopressin (DDAVP), a synthetic antidiuretic hormone analogue that has no vasoconstrictive effects. DDAVP transiently increases von Willebrand factor and factor VIII release from endothelial cell storage through indirect mechanisms; it can be used prophylactically prior to procedures or to treat minor bleeding.

References

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References

- Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years.

Pharmacology	Hematology & Oncology	Von willebrand disease
Subject	System	Topic

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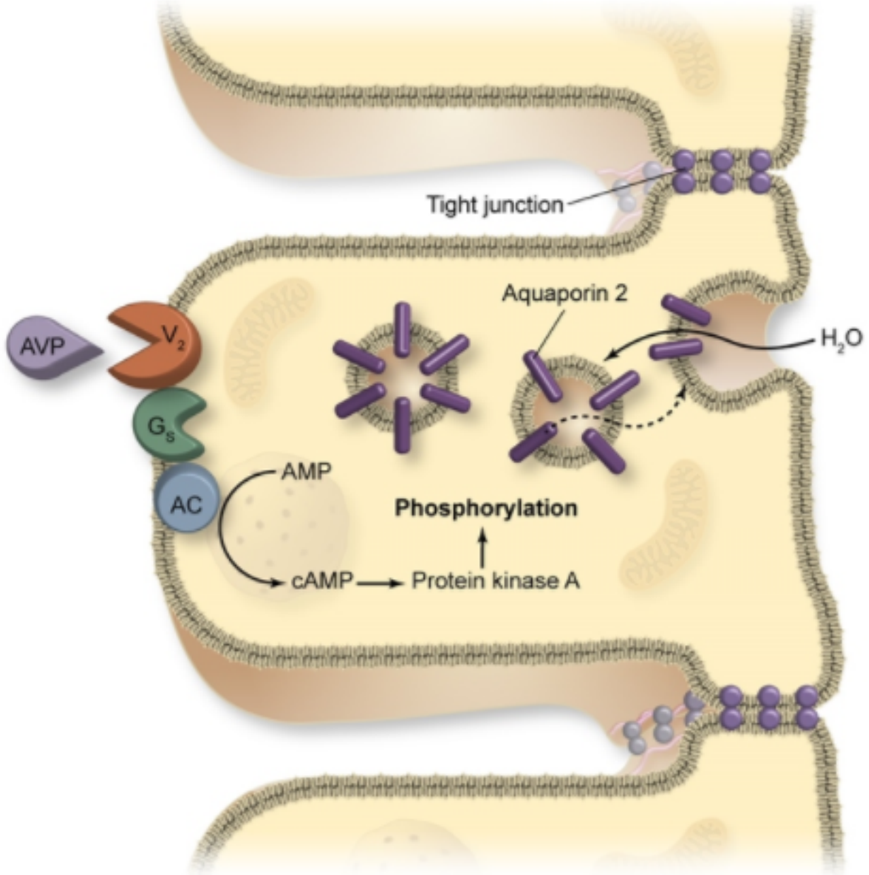
(whose half-life is tremendously shortened when not bound to VWF).

Exhibit Display

ADH action on collecting duct



AC = adenylyl cyclase; ADH = antidiuretic hormone; AVP = arginine vasopressin; cAMP = cyclic AMP.
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Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

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A 52-year-old man recovering from an acute myocardial infarction develops new-onset chest pain that is relieved by leaning forward. The pain is exacerbated with deep inspiration. The patient was admitted with acute inferior myocardial infarction 2 days ago and did not undergo revascularization due to his late presentation. Since admission, he has had no chest pain until this morning. On physical examination, a friction rub is present at the left sternal border. The patient is treated with a medication that inhibits COX-1 and COX-2 enzymes via irreversible acetylation, resulting in significant relief of his symptoms. Which of the following agents was most likely used in this patient?

- A. Acetaminophen
- B. Aspirin
- C. Budesonide
- D. Celecoxib
- E. Colchicine
- F. Diclofenac
- G. Ibuprofen
- H. Indomethacin

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A. Acetaminophen (1%)
✓ B. Aspirin (91%)
C. Budesonide (0%)
D. Celecoxib (2%)
E. Colchicine (0%)
F. Diclofenac (0%)
G. Ibuprofen (1%)
H. Indomethacin (1%)

Omitted
Correct answer
B

91%
Answered correctly

02 secs
Time Spent

03/25/2020
Last Updated

Explanation

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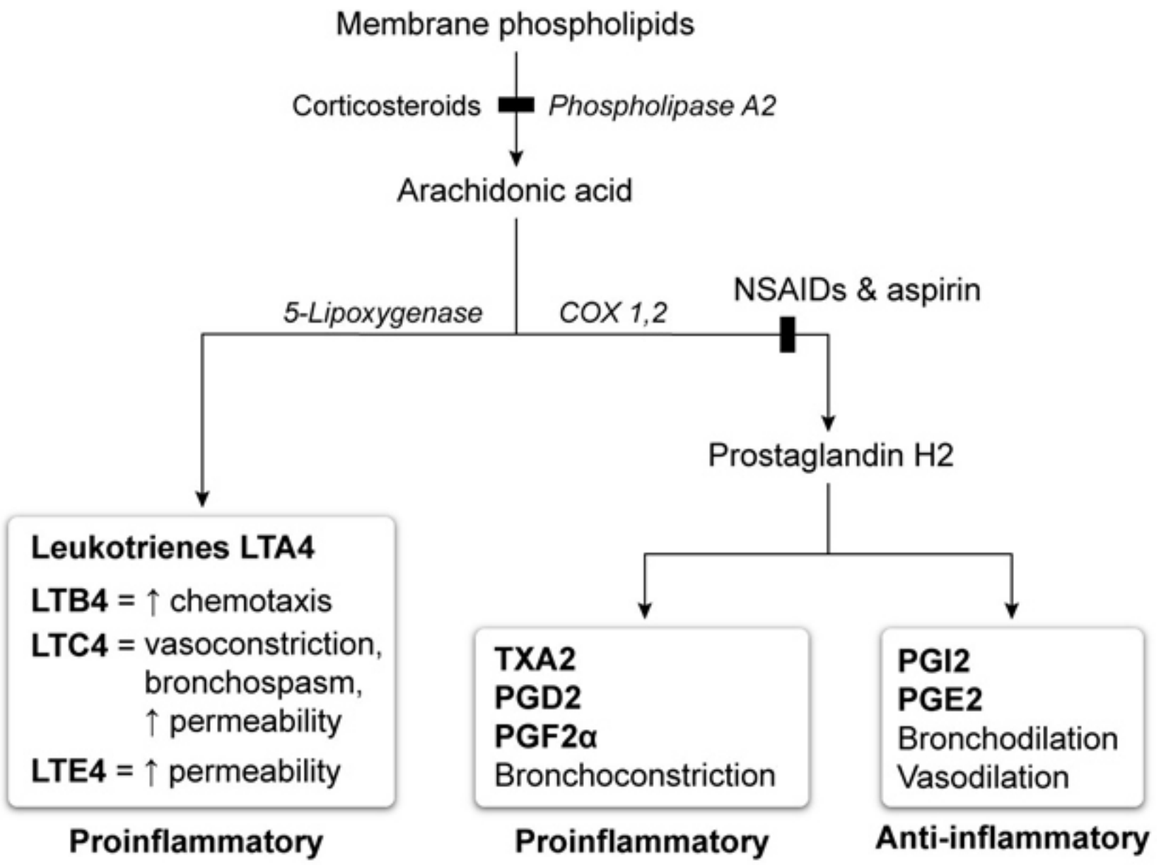
Arachidonic acid metabolic pathways



COX = cyclooxygenase-2; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PG** = prostaglandin; **TXA** = tranexamic acid.

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This patient's presentation of recent (within 1-3 days) myocardial infarction, pleuritic chest pain improved by leaning forward, and a friction rub on cardiac examination likely indicates peri-infarction pericarditis. Although most patients with peri-infarction pericarditis improve with supportive measures, those with sufficient or persistent symptoms are typically treated with aspirin in combination with colchicine.

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Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that **irreversibly inhibits** cyclooxygenase-1 and -2 (**COX-1 and -2**) enzymes via **acetylation**, preventing conversion of arachidonic acid to prostaglandins, prostacyclin, and thromboxane. COX-1 acetylation inhibits generation of thromboxane A_2 in platelets (antithrombotic effect). COX-2 acetylation blocks prostaglandin production in inflammatory cells (eg, activated lymphocytes, neutrophils), resulting in anti-inflammatory, antipyretic, and analgesic effects.

(Choice A) Acetaminophen is an analgesic and antipyretic agent that reversibly inhibits COX enzymes (primarily in the central nervous system). It lacks anti-inflammatory properties due to its weak inhibition of COX in peripheral tissues.

(Choice C) Budesonide is a glucocorticoid agent with potent anti-inflammatory activity. Corticosteroids reduce COX-2 expression and decrease synthesis of arachidonic acid via phospholipase A_2 inhibition.

(Choice D) Celecoxib is a selective COX-2 inhibitor that provides anti-inflammatory benefits without interfering with the physiological functions of COX-1. In contrast to the non-selective NSAIDs, selective COX-2 inhibitors have no significant effect on platelet function and are associated with a lower incidence of gastrointestinal bleeding. However, selective COX-2 inhibition is associated with an increased incidence of thrombosis.

(Choice E) Colchicine exerts its anti-inflammatory effects by inhibiting polymerization of beta-tubulin into microtubules, preventing migration and activation of neutrophils.

(Choices F, G, and H) Diclofenac, ibuprofen, and indomethacin are NSAIDs that **reversibly** inhibit COX-1 and COX-2.

Educational objective:
Aspirin (acetylsalicylic acid) is a nonsteroidal anti-inflammatory drug (NSAID) that irreversibly inhibits cyclooxygenase-1 and -2 (COX-1 and -2) enzymes via acetylation. In contrast, other NSAIDs (eg, diclofenac, ibuprofen, indomethacin) reversibly inhibit COX-1 and COX-2.

References

- Clinical pharmacology of non-steroidal anti-inflammatory drugs: A review.
- What are all the things that aspirin does?

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A 56-year-old man comes to the emergency department due to right lower extremity pain and swelling. The symptoms began shortly after he flew back to the United States from a 7-day cruise in Indonesia. Doppler ultrasonography reveals a femoropopliteal venous thrombosis, and the patient is given anticoagulation with rivaroxaban. Compared to vitamin K antagonists, this patient's treatment is most likely to have which of the following benefits?

- A. Better patient compliance
- B. Greater efficacy
- C. Less risk of thrombocytopenia
- D. No need for loading dose
- E. Less variability in therapeutic effect

Submit

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- A. Better patient compliance (9%)
- B. Greater efficacy (6%)
- C. Less risk of thrombocytopenia (11%)
- D. No need for loading dose (15%)
- ✓ E. Less variability in therapeutic effect (56%)

Omitted
Correct answer
E

56%
Answered correctly

01 sec
Time Spent

04/14/2020
Last Updated

Explanation

Direct oral anticoagulants (DOACs) versus warfarin		
	DOACs	**Warfarin**
Dosing	>1 dose daily may be required	Once daily
Dietary restrictions	None	Stable vitamin K intake required

Direct oral anticoagulants (DOACs) versus warfarin		
	DOACs	**Warfarin**
Dosing	>1 dose daily may be required	Once daily
Dietary restrictions	None	Stable vitamin K intake required
Drug interactions	Few	Many
Required monitoring	None	INR
Comorbid conditions	Renal failure may prohibit use	No prohibitions

Rivaroxaban is a direct oral anticoagulant (DOAC) that binds to and **inhibits factor Xa**, thereby preventing conversion of prothrombin to thrombin. DOACs are generally preferred over vitamin K antagonists (VKAs) such as warfarin for most conditions requiring prolonged anticoagulation due to **less variability in therapeutic effect**.

The therapeutic effect of VKAs is affected by changes to dietary intake of vitamin K, disruption to vitamin K– producing intestinal flora (eg, antibiotics), and a wide range of medications that inhibit or induce cytochrome P450 2C9; therefore, patients given VKAs require coagulation monitoring (eg, with INR) to ensure adequate anticoagulation. In contrast, the therapeutic effect of DOACs is not typically altered by environmental or medication changes; therefore, **laboratory monitoring is not required**. DOACs may also have a lower risk of intracranial bleeding, the most serious risk of anticoagulation, when compared to VKAs.

(Choice A) Rates of patient compliance are roughly equivalent for DOACs and VKAs.

(Choices B and C) Heparin can cause thrombocytopenia due to either heparin-induced thrombocytopenia type I (nonimmune mediated) or type 2 (immune mediated). VKAs target vitamin K–dependent clotting factors (not platelets), so they do not typically cause thrombocytopenia. VKAs and DOACs have roughly the same efficacy.

(Choice D) A loading dose is required with heparin. Some DOACs (eg, rivaroxaban) also require a higher dose for the first few weeks prior to initiating a lower maintenance dose. VKAs do not require a loading dose.

Comorbid conditions	Renal failure may prohibit use	No prohibitions

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The therapeutic effect of VKAs is affected by changes to dietary intake of vitamin K, disruption to vitamin K– producing intestinal flora (eg, antibiotics), and a wide range of medications that inhibit or induce cytochrome P450 2C9; therefore, patients given VKAs require coagulation monitoring (eg, with INR) to ensure adequate anticoagulation. In contrast, the therapeutic effect of DOACs is not typically altered by environmental or medication changes; therefore, **laboratory monitoring is not required**. DOACs may also have a lower risk of intracranial bleeding, the most serious risk of anticoagulation, when compared to VKAs.

(Choice A) Rates of patient compliance are roughly equivalent for DOACs and VKAs.

(Choices B and C) Heparin can cause thrombocytopenia due to either heparin-induced thrombocytopenia type I (nonimmune mediated) or type 2 (immune mediated). VKAs target vitamin K–dependent clotting factors (not platelets), so they do not typically cause thrombocytopenia. VKAs and DOACs have roughly the same efficacy.

(Choice D) A loading dose is required with heparin. Some DOACs (eg, rivaroxaban) also require a higher dose for the first few weeks prior to initiating a lower maintenance dose. VKAs do not require a loading dose.

Educational objective:
Direct oral anticoagulants (DOACs) such as rivaroxaban are often preferred over vitamin K antagonists (VKAs) such as warfarin in the treatment of conditions that require anticoagulation due to less variability in therapeutic drug effect; in contrast to VKAs, the efficacy of DOACs is unaffected by dietary changes and most medications. Therefore, patients given DOACs do not require laboratory monitoring.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 44-year-old male is hospitalized with unstable angina. On the fourth day of hospitalization he develops severe foot pain and right toe paleness. His laboratory testing is significant for platelet count of 60,000/mm^3. Treatment with argatroban is initiated immediately. The drug (argatroban) used to treat this patient's current condition has which mechanism of action?

A. Binds to the thrombin active site

B. Blocks glutamate residue carboxylation

C. Block ADP receptors

D. Block GP IIb/IIIa surface receptors

E. Inhibits phosphodiesterase

Submit

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- ✓ A. Binds to the thrombin active site (50%)
- B. Blocks glutamate residue carboxylation (4%)
- C. Block ADP receptors (15%)
- D. Block GP IIb/IIIa surface receptors (22%)
- E. Inhibits phosphodiesterase (6%)

Omitted
Correct answer
A

50%
Answered correctly

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Time Spent

06/20/2020
Last Updated

Explanation

Heparin is the most important cause of thrombocytopenia in hospitalized patients. Occurrence of heparin-induced thrombocytopenia (HIT) is much more common with the use of unfractionated heparin compared to low molecular weight heparin. HIT more commonly leads to paradoxical thrombosis rather than bleeding. HIT is a serious disorder caused by antibodies to heparin and platelet factor IV.

Direct thrombin inhibitors (hirudin, lepirudin and argatroban) do not require antithrombin-III for their action and are drugs of choice in the treatment of HIT. Patients with HIT need ongoing anticoagulation due to the presence of, or possibility of thrombosis. Upon clinical suspicion of HIT, the most important initial step in treatment is to stop all forms of heparin.

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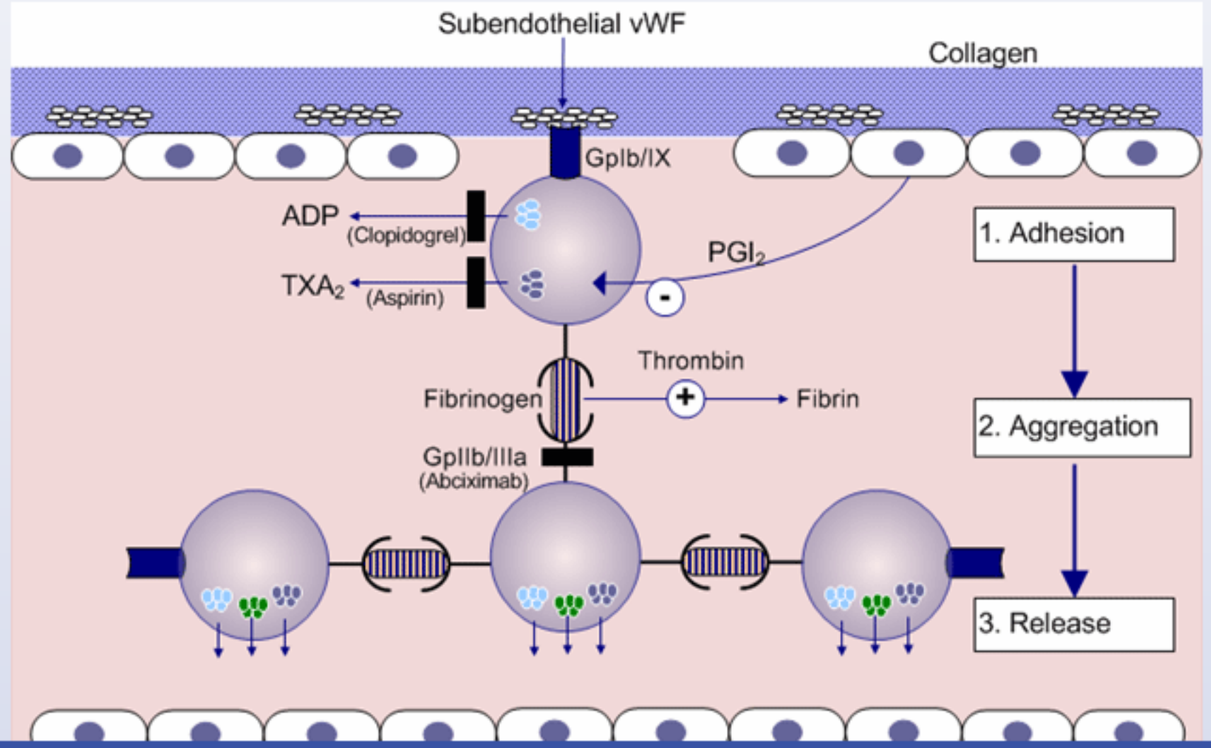
(Choice B) Warfarin inhibits vitamin K dependent γ-carboxylation of glutamic acid residues of clotting factors II, VII, IX and X.

(Choices C, D and E) Platelet plug formation involves three critical steps: adhesion, aggregation and release (see diagram). Drugs that inhibit platelet aggregation work by different mechanisms.



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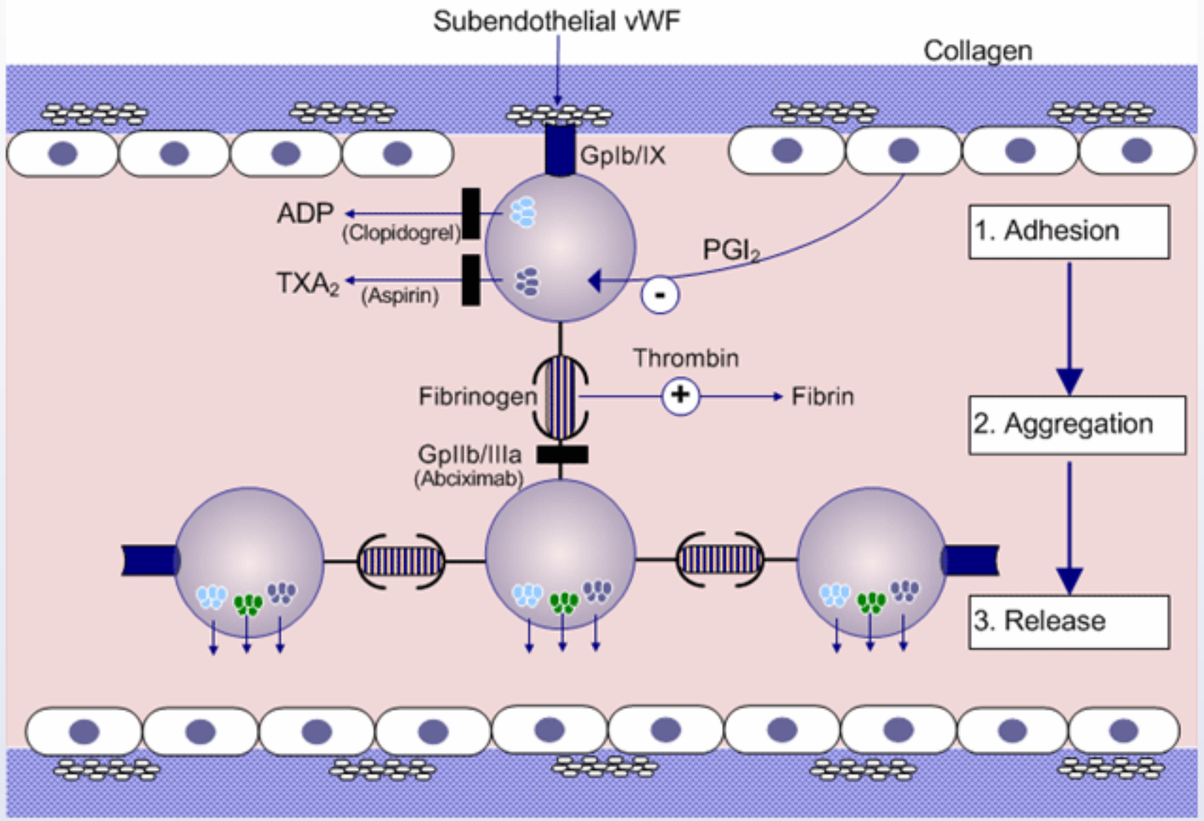
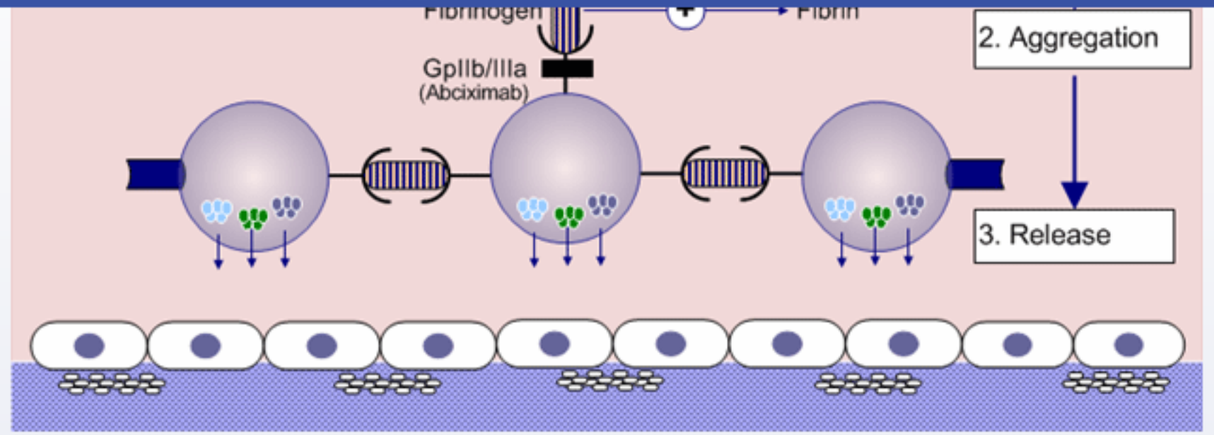


Aspirin irreversibly acetylates platelet cyclooxygenase-I leading to decreased formation of thromboxane A2. Aspirin is used for primary and secondary prevention of myocardial infarction and strokes.

Ticlopidine and clopidogrel inhibit ADP mediated platelet aggregation. They are useful following percutaneous coronary intervention (PCI), and for treatment of unstable angina and non-Q wave myocardial infarction.

Dipyridamole and cilostazol inhibit platelet aggregation by inhibiting phosphodiesterase activity and increasing cAMP.

Glycoprotein IIb/IIIa inhibitors inhibit binding of platelet glycoprotein IIb/IIIa with fibrinogen and fibronectin. The glycoprotein IIb/IIIa inhibitors abciximab, eptifibatide and tirofiban are approved for use following percutaneous intervention (PCI) in acute coronary syndrome.



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Educational objective:
Heparin-induced thrombocytopenia (HIT) is treated with direct thrombin inhibitors (DTIs) such as argatroban. Both high molecular weight heparin and LMWH should be avoided in these patients.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 62-year-old woman comes to the office due to a painless neck mass that has gradually enlarged over several months. She also has had fatigue, night sweats, and unintentional weight loss. Physical examination shows rubbery, nontender, bilateral cervical lymphadenopathy. Imaging studies reveal mediastinal and abdominal lymphadenopathy, and subsequent excisional lymph node biopsy is consistent with diffuse large B cell lymphoma. The patient receives combination chemotherapy, which leads to rapid lysis of neoplastic cells. She also receives rasburicase prior to and during treatment. This medication helps to protect normal organs by which of the following mechanisms?

A. Converting uric acid into more soluble metabolites

B. Forming insoluble complexes with phosphate

C. Inhibiting uric acid formation after cell lysis

D. Supplying a thiol group to inactivate toxic metabolites

E. Supplying necessary cofactors blocked by a chemotherapeutic agent

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- ✓ A. Converting uric acid into more soluble metabolites (78%)
- B. Forming insoluble complexes with phosphate (1%)
- C. Inhibiting uric acid formation after cell lysis (13%)
- D. Supplying a thiol group to inactivate toxic metabolites (4%)
- E. Supplying necessary cofactors blocked by a chemotherapeutic agent (1%)

Omitted
Correct answer
A

78%
Answered correctly

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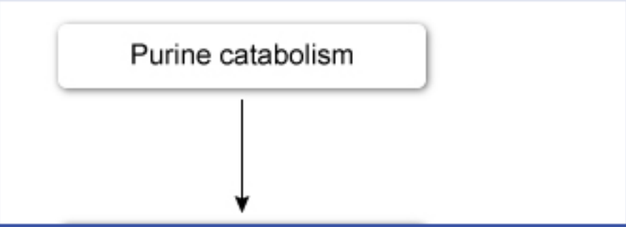
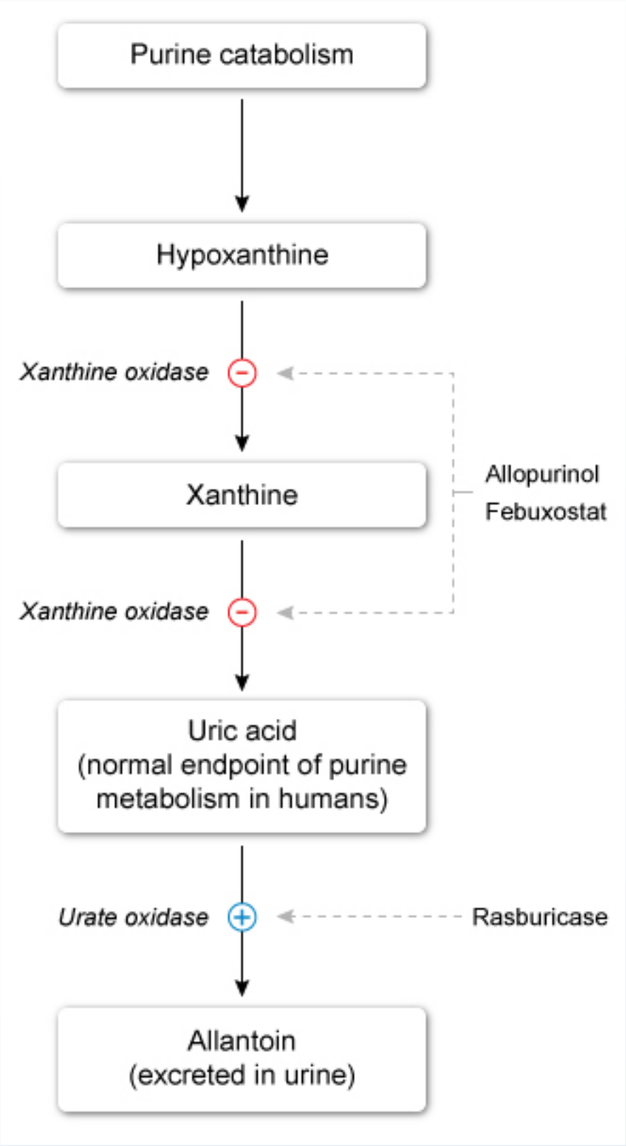
Time Spent

05/11/2020
Last Updated

Explanation





Tumor lysis syndrome (TLS) is an oncologic emergency that primarily develops during initial chemotherapy for high-grade lymphomas,

Tumor lysis syndrome (TLS) is an oncologic emergency that primarily develops during initial chemotherapy for high-grade lymphomas, leukemias, and other cancers with rapid cell turnover, substantial tumor burden, or high sensitivity to chemotherapy. When large numbers of tumor cells are destroyed in a short period, massive quantities of intracellular tumor products are released into the circulation, which frequently results in the following:

- Hyperkalemia, which can cause fatal heart arrhythmias.
- Hyperphosphatemia, which precipitates calcium in the renal tubules and collecting system, leading to systemic hypocalcemia and acute renal injury from calcium-phosphate stones.
- Hyperuricemia, which precipitates urate crystals in the renal tubules and collecting system, leading to acute renal injury.

Aggressive **intravenous fluids** during and after chemotherapy can help prevent kidney injury by flushing phosphorous and uric acid out of the kidneys. Treatment with an agent that reduces the formation of uric acid is also generally required to limit the formation of uric acid stones, including 1 of the following:

- **Rasburicase** is a recombinant version of **urate oxidase**, an enzyme present in many mammals, but not in humans. Urate oxidase converts uric acid into **allantoin**, a purine metabolite that is 5-10 times **more soluble** than uric acid and therefore far less likely to precipitate in the kidney.
- Allopurinol is a purine decoy that competitively inhibits xanthine oxidase (and other enzymes involved in purine metabolism), which reduces the conversion of purine metabolites into xanthine and uric acid **(Choice C)**. Febuxostat is a non-purine selective inhibitor of xanthine oxidase; it is similar to allopurinol, but it has fewer adverse effects and drug interactions.

(Choice B) Phosphate binders (eg, sevelamer) are used to manage hyperphosphatemia in patients with chronic kidney disease. Rasburicase does not target phosphate.

(Choice D) Mesna can prevent hemorrhagic cystitis in patients receiving cyclophosphamide or ifosfamide; it supplies a thiol group that inactivates the toxic metabolite (acrolein) of these chemotherapeutic agents.

(Choice E) Folinic acid (leucovorin) provides a reduced form of folic acid to counter the methotrexate-induced block in folic acid metabolism. It "rescues" gastrointestinal mucosa and bone marrow cells from the effects of methotrexate (which causes cell death in rapidly dividing cells).

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Educational objective:
Tumor lysis syndrome primarily develops during chemotherapy for cancers with rapid cell turnover, substantial tumor burden, or high sensitivity to chemotherapy. It is characterized by hyperphosphatemia, hypocalcemia, hyperkalemia, and hyperuricemia. Prevention involves intravenous fluids to flush the kidneys and the use of hypouricemic agents (eg, rasburicase, allopurinol, febuxostat).

References

- Rasburicase for the treatment of tumor lysis in hematological malignancies.

Pharmacology	Hematology & Oncology	Tumor lysis syndrome
Subject	System	Topic

Aggressive **intravenous fluids** during and after chemotherapy can help prevent kidney injury by flushing phosphorous and uric acid out of the

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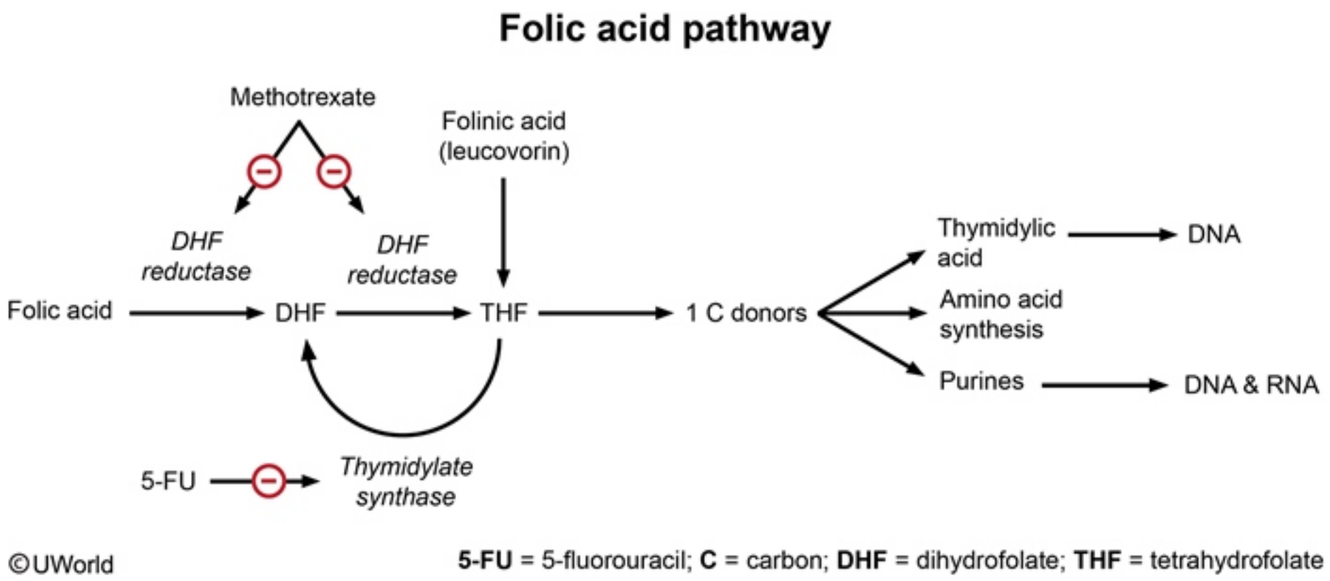

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A 23-year-old woman with a history of sickle cell disease comes to the office for follow-up. The patient is homozygous for hemoglobin S and has had frequent episodes of painful vasoocclusive crises. She has no other medical conditions and takes folic acid supplementation. The patient does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Additional therapy with hydroxyurea is planned. This medication is likely to improve this patient's symptoms primarily through which of the following mechanisms?

A. Decreased red blood cell dehydration

B. Direct inhibition of red blood cell polymerization

C. Increased hemoglobin A2 synthesis

D. Increased fetal hemoglobin synthesis

E. Increased red blood cell antioxidant levels

F. Stimulation of red blood cell production

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- A. Decreased red blood cell dehydration (1%)
- B. Direct inhibition of red blood cell polymerization (5%)
- C. Increased hemoglobin A2 synthesis (1%)
- ✓ D. Increased fetal hemoglobin synthesis (88%)
- E. Increased red blood cell antioxidant levels (1%)
- F. Stimulation of red blood cell production (0%)

Omitted
Correct answer
D

88%
Answered correctly

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Time Spent

05/11/2020
Last Updated

Explanation

Main adult hemoglobin

Hemoglobin A (alpha$_2$ beta$_2$)

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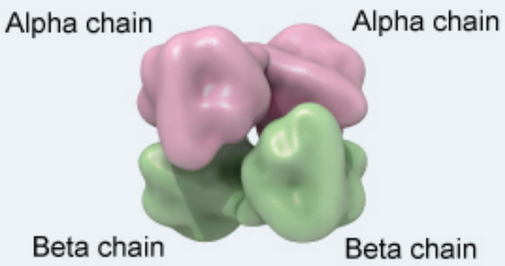
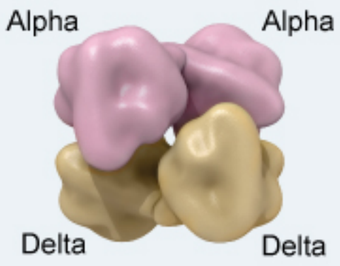
Main adult hemoglobin

Hemoglobin A ($alpha_2$ $beta_2$)

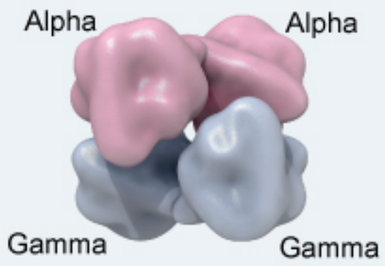


Hemoglobin variants

Hemoglobin A2 ($alpha_2$ $delta_2$)



Hemoglobin F ($alpha_2$ $gamma_2$)



Hemoglobin H ($beta_4$)

Hemoglobin Bart's ($gamma_4$)

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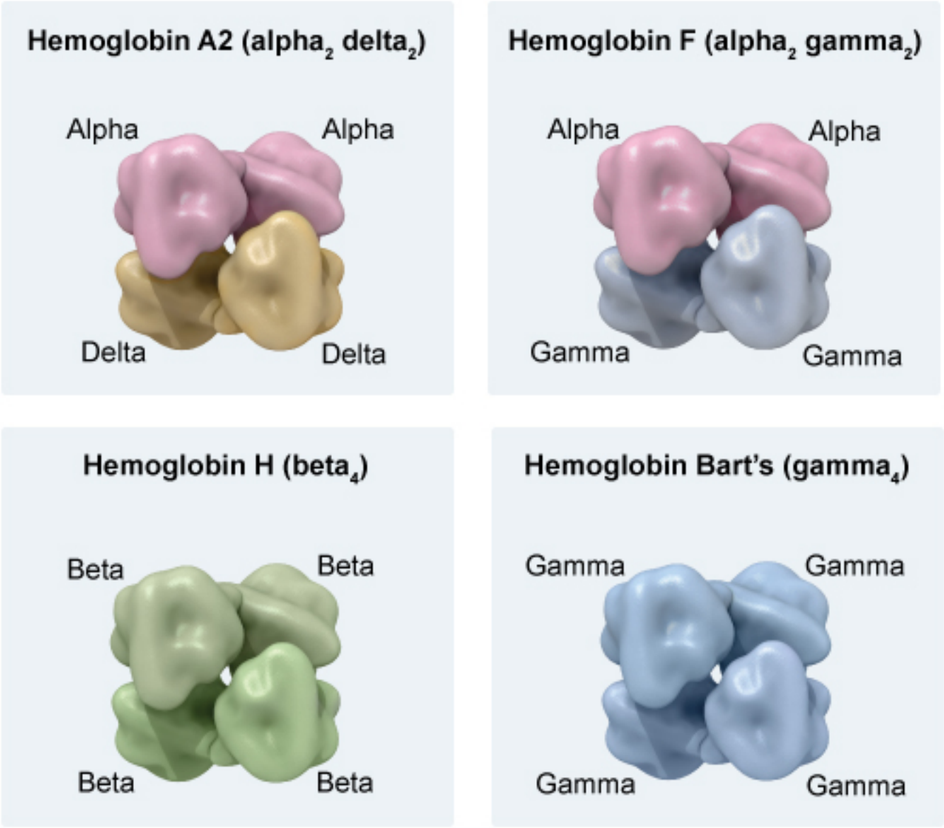
Hemoglobin variants



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Patients with **sickle cell disease** (SCD) have a missense mutation in the beta globin gene that leads to the substitution of valine for glutamic acid in the 6th position of the beta globulin chain. This altered form of hemoglobin is called **hemoglobin S** (Hb S); unlike normal adult hemoglobin (Hb A), Hb S polymerizes when deoxygenated or dehydrated, leading to erythrocyte membrane damage (ie, intravascular **hemolysis**) and clogging of small vessels (ie, painful **vasoocclusive crises**, ischemia).

Heterozygotes for Hb S are usually asymptomatic because there is enough Hb A to prevent extensive polymerization of Hb S, but homozygotes

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Heterozygotes for Hb S are usually asymptomatic because there is enough Hb A to prevent extensive polymerization of Hb S, but homozygotes typically have severe disease. These individuals often require repeated blood transfusions for symptomatic anemia and treatment with **hydroxyurea**, an antimetabolite that inhibits the ribonucleotide reductase enzyme. Although inhibition of ribonucleotide reductase leads to the myelosuppressive effects of hydroxyurea (it causes cell cycle arrest in rapidly dividing hematopoietic cells), hydroxyurea also shifts globin gene transcription from the beta globin locus to the **gamma globin** locus (via unclear mechanisms), thereby **increasing** circulating levels of **fetal hemoglobin** (HB F).

HB F is unaffected by the sickle cell mutation (because it is not composed of beta chains) and has physiologic properties similar to hemoglobin A; therefore, hydroxyurea is often used in the treatment of SCD to improve oxygen delivery, reduce vasoocclusive crises, and lessen need for transfusions.

(Choice A) The calcium-dependent (Gardos) potassium channel regulates the transport of potassium and water through the erythrocyte membrane; blocking this channel could help prevent erythrocyte dehydration but has not been shown to improve symptoms.

(Choice B) Voxelotor directly inhibits polymerization of Hb S by binding to the alpha chain of the molecule and causing an allosteric change that results in increased oxygen binding.

(Choice C) Hb A2 is a variant of normal adult hemoglobin that has 2 delta chains instead of 2 beta chains. Because it does not contain the abnormal beta chains, increased hemoglobin A2 could reduce sickle cell crises. However, hydroxyurea increases gamma globulin expression, not delta globulin expression.

(Choice E) L-glutamine, a precursor to the antioxidant glutathione, reduces oxidative stress in erythrocytes with HB S. It is used for patients with SCD who have persistent vasoocclusive pain or those who cannot tolerate hydroxyurea.

(Choice F) Stimulation of erythrocyte production (eg, erythropoietin) would likely worsen vasoocclusive crises by increasing circulating levels of Hb S. Hydroxyurea inhibits (not stimulates) the production of erythrocytes, leukocytes, and platelets by blocking ribonucleotide reductase.

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(Choice F) Stimulation of erythrocyte production (eg, erythropoietin) would likely worsen vasoocclusive crises by increasing circulating levels of Hb S. Hydroxyurea inhibits (not stimulates) the production of erythrocytes, leukocytes, and platelets by blocking ribonucleotide reductase; however, patients with SCD still benefit from administration due to stimulated HB F production.

Educational objective:
Hydroxyurea is used in patients with sickle cell disease to increase expression of gamma globin chains, which leads to increased circulating fetal hemoglobin (Hb F) concentration. This reduces vasoocclusive crises and symptomatic anemia episodes.

Pharmacology	Hematology & Oncology	Sickle cell
Subject	System	Topic

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In vitro studies demonstrate that tumor cell lines can become resistant after exposure to various anticancer agents. These cells express a specific cell surface glycoprotein that has which of the following functions?

A. Tyrosine kinase-coupled receptor

B. Adenylate cyclase-coupled receptor

C. Cell adhesion molecule

D. Transmembrane ion channel

E. ATP-dependent transporter

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In vitro studies demonstrate that tumor cell lines can become resistant after exposure to various anticancer agents. These cells express a specific cell surface glycoprotein that has which of the following functions?

A. Tyrosine kinase-coupled receptor (29%)

B. Adenylate cyclase-coupled receptor (8%)

C. Cell adhesion molecule (17%)

D. Transmembrane ion channel (10%)

✓ E. ATP-dependent transporter (32%)

Omitted
Correct answer
E

32%
Answered correctly

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Time Spent

02/03/2020
Last Updated

Explanation

Human tumor cells have developed the ability to resist chemotherapy in much the same way that many bacteria have developed resistance to antibiotics. One well-studied mechanism by which human tumor cells resist these agents is via the human multidrug resistance (MDR1) gene. The prototype product of this gene is P-glycoprotein, a transmembrane protein that functions as an ATP-dependent efflux pump. P-glycoprotein is normally expressed in intestinal and renal tubular epithelial cells and functions to eliminate foreign compounds from the body. This protein is also present in the capillary endothelium of the vessels that form the blood-brain barrier. In this location, P-glycoprotein prevents the penetration of foreign compounds into the CNS. In tumor cells, this ATP-powered transmembrane pump protein actively removes chemotherapeutic agents, particularly hydrophobic agents like the anthracyclines.

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Drugs such as verapamil, diltiazem, and ketoconazole, among others, have been shown to reduce the action of this multidrug resistance protein in experimental models; the development of agents specifically intended to abolish this mechanism of resistance is currently underway.

(Choice A) Tyrosine kinase receptors generally mediate the effects of hormones that promote anabolism and cell growth such as insulin, insulin-like growth factor 1, epidermal growth factor, platelet-derived growth factor, and others.

(Choice B) cAMP is the second messenger in the G-protein / adenylate cyclase second messenger system. This system is utilized by numerous hormone receptors including beta-adrenergic receptors, V2 ADH receptors, and calcitonin, glucagon, TSH, ACTH, and HCG receptors, among many others.

(Choice C) Cell adhesion molecules (CAMs) are proteins located on the cell surface that mediate binding with other cells or with the extracellular matrix. Examples include selectins, integrins, and cadherins. Cell adhesion molecules are generally downregulated in malignant tumors, which allows these cells to spread from their site of origin.

(Choice D) Transmembrane ion channels selectively allow certain ions to pass into or out of the cell. These channels facilitate the formation of a voltage gradient across the cell membrane. Examples of ion channels, transporters, and exchangers are ubiquitous. These proteins participate in the formation of urine, nerve and myocyte depolarization, muscle contraction, sweat formation, exocrine secretion formation, and many other processes.

Educational Objective:
The human multidrug resistance (MDR1) gene codes for P-glycoprotein, a transmembrane ATP-dependent efflux pump protein that has a broad specificity for hydrophobic compounds. This protein can both reduce the influx of drugs into the cytosol and can increase efflux from the cytosol,

foreign compounds into the CNS. In tumor cells, this ATP-powered transmembrane pump protein actively removes chemotherapeutic agents, particularly hydrophobic agents like the anthracyclines.

Drugs such as verapamil, diltiazem, and ketoconazole, among others, have been shown to reduce the action of this multidrug resistance protein in experimental models; the development of agents specifically intended to abolish this mechanism of resistance is currently underway.

(Choice A) Tyrosine kinase receptors generally mediate the effects of hormones that promote anabolism and cell growth such as insulin, insulin-like growth factor 1, epidermal growth factor, platelet-derived growth factor, and others.

(Choice B) cAMP is the second messenger in the G-protein / adenylate cyclase second messenger system. This system is utilized by numerous hormone receptors including beta-adrenergic receptors, V2 ADH receptors, and calcitonin, glucagon, TSH, ACTH, and HCG receptors, among many others.

(Choice C) Cell adhesion molecules (CAMs) are proteins located on the cell surface that mediate binding with other cells or with the extracellular matrix. Examples include selectins, integrins, and cadherins. Cell adhesion molecules are generally downregulated in malignant tumors, which allows these cells to spread from their site of origin.

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Educational Objective:
The human multidrug resistance (MDR1) gene codes for P-glycoprotein, a transmembrane ATP-dependent efflux pump protein that has a broad specificity for hydrophobic compounds. This protein can both reduce the influx of drugs into the cytosol and can increase efflux from the cytosol, thereby preventing the action of chemotherapeutic agents.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 52-year-old woman comes to the office due to 2 weeks of constant back pain. She has also had several months of nonproductive cough, anorexia, and unintentional weight loss. The patient has a 40-pack-year smoking history. Physical examination shows diffuse muscle wasting, left lung crackles, and vertebral tenderness. Imaging reveals a left lung mass and lytic lesions in the vertebrae. Further evaluation confirms metastatic non-small cell lung cancer. Treatment with a cisplatin-based chemotherapy is begun, and the patient is also started on a neurokinin-1 receptor antagonist. The latter medication is most likely to improve which of the following in this patient?

A. Chemotherapy-induced nausea

B. Malignancy-related anorexia

C. Metastases-related hypercalcemia

D. Opioid-induced constipation

E. Tumor lysis-induced renal failure

Submit

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- ✓ A. Chemotherapy-induced nausea (84%)
- B. Malignancy-related anorexia (4%)
- C. Metastases-related hypercalcemia (2%)
- D. Opioid-induced constipation (1%)
- E. Tumor lysis-induced renal failure (6%)

Omitted
Correct answer
A

84%
Answered correctly

02 secs
Time Spent

02/24/2020
Last Updated

Explanation

Common antiemetic drugs			
Drug class	**Examples**	**Clinical uses**	**Major side effects**
Antimuscarinics (anticholinergics)	• Scopolamine	• Vestibular nausea	• Anticholinergic effects (eg, dry mouth,

Explanation

Common antiemetic drugs			
Drug class	**Examples**	**Clinical uses**	**Major side effects**
Antimuscarinics (anticholinergics)	• Scopolamine	• Vestibular nausea • Motion sickness	• Anticholinergic effects (eg, dry mouth, sedation)
Antihistamines	• Meclizine		
Dopamine receptor antagonists (DRAs)	• Prochlorperazine • Metoclopramide • Chlorpromazine	• Migraine headache (DRAs) • Acute or chronic nausea/vomiting • Acute chemotherapy-induced emesis	• Extrapyramidal reactions
Serotonin (5-HT_3) receptor antagonists	• Ondansetron • Granisetron		• QT prolongation
Neurokinin-1 (NK1) receptor antagonists	• Aprepitant • Fosaprepitant	• Delayed chemotherapy-induced emesis	• Neutropenia

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of cancer treatment. It is caused by both peripheral and central mechanisms, as follows:

- **Acute-phase CINV** (<24 hours after chemotherapy) is mediated primarily by the release of **serotonin** from intestinal enterochromaffin cells that have been damaged by chemotherapy. Serotonin stimulates vagal afferent fibers (5-HT3 receptors) in the bowel wall, which project to the brainstem and stimulate the vomiting reflex. Therefore, **serotonin receptor antagonists** (eg, ondansetron) can be used for treatment.
- **Delayed-phase CINV** (1-5 days after chemotherapy) is mediated primarily by increased levels of **substance P** in the brainstem due to chemotherapy-associated emetic stimuli in the cerebrospinal fluid and bloodstream. Substance P binds to and activates the **neurokinin-1** (NK1) **receptor** in areas of the brainstem that mediate vomiting (eg, nucleus tractus solitarius, area postrema). Therefore, **NK1 receptor antagonists** (eg, aprepitant, fosaprepitant) are often used for treatment.

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Most patients who undergo chemotherapy associated with a high risk of vomiting (eg, cisplatin) receive a combination of serotonin receptor antagonists and NK1 receptor antagonists (often with other antiemetics) to prevent both types of CINV.

(Choice B) Malignancy-related anorexia is the loss of muscle and fat caused by elevated levels of circulating inflammatory cytokines. Progesterone analogs (eg, megestrol acetate) are the first-line treatment; corticosteroids and cannabinoids are also frequently used.

(Choice C) Malignancy-related hypercalcemia is typically treated with bisphosphonates (eg, zoledronic acid), which reduce osteoclast-mediated bone resorption.

(Choice D) Opioid-induced constipation occurs due to opioid-mediated effects on the bowel wall, which reduce peristalsis. Methylnaltrexone, an opioid antagonist that has limited ability to cross the blood-brain barrier (it does not trigger withdrawal), can be used as treatment.

(Choice E) Patients who have highly aggressive lymphomas and leukemias are at risk for tumor lysis syndrome (TLS) with chemotherapy. Its primary manifestation is renal damage from elevated uric acid levels (catabolism of nucleic acids released from tumor cells increases uric acid). Rasburicase, a drug that breaks down uric acid, is used to prevent TLS in high-risk patients.

Educational objective:
Chemotherapy-induced nausea and vomiting is mediated by peripheral and central mechanisms. It can be treated with serotonin receptor antagonists (eg, ondansetron) to prevent serotonin stimulation of afferent vagal fibers in the bowel wall (peripheral cause) and neurokinin-1 receptor antagonists (eg, aprepitant) to prevent the effects of substance P in the brainstem (central cause).

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Chemotherapy-induced nausea and vomiting is mediated by peripheral and central mechanisms. It can be treated with serotonin receptor antagonists (eg, ondansetron) to prevent serotonin stimulation of afferent vagal fibers in the bowel wall (peripheral cause) and neurokinin-1 receptor antagonists (eg, aprepitant) to prevent the effects of substance P in the brainstem (central cause).

Pharmacology	Hematology & Oncology	Chemotherapy induced nausea and vomiting
Subject	System	Topic

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A 56-year-old woman comes to the emergency department due to 3 days of frequent urination, suprapubic pain, dysuria, and progressive hematuria. She has had no fevers or chills. The patient has a history of lymph-node-positive breast cancer that was diagnosed following a routine mammogram. A month ago, she began treatment with systemic chemotherapy. Temperature is 37.1 C (98.8 F). Suprapubic tenderness is present on abdominal examination. Hemoglobin is 9.8 g/dL. Urinalysis shows numerous red blood cells but no leukocyte esterase or bacteria. Which of the following could have prevented this patient's current condition?

A. Dexrazoxane
B. Filgrastim
C. Folinic acid
D. Mesna
E. Ondansetron

Submit

A 56-year-old woman comes to the emergency department due to 3 days of frequent urination, suprapubic pain, dysuria, and progressive hematuria. She has had no fevers or chills. The patient has a history of lymph-node-positive breast cancer that was diagnosed following a routine mammogram. A month ago, she began treatment with systemic chemotherapy. Temperature is 37.1 C (98.8 F). Suprapubic tenderness is present on abdominal examination. Hemoglobin is 9.8 g/dL. Urinalysis shows numerous red blood cells but no leukocyte esterase or bacteria. Which of the following could have prevented this patient's current condition?

- A. Dexrazoxane (4%)
- B. Filgrastim (7%)
- C. Folinic acid (9%)
- ✓ D. Mesna (75%)
- E. Ondansetron (2%)

Omitted
Correct answer
D

75%
Answered correctly

02 secs
Time Spent

04/22/2020
Last Updated

Explanation

This patient who recently received systemic chemotherapy for breast cancer and now has progressive hematuria and suprapubic tenderness most likely has **hemorrhagic cystitis** caused by a nitrogen mustard-based chemotherapeutic agent, such as **cyclophosphamide** or one of its analogs (eg, ifosfamide). These agents are metabolized by the kidneys into **acrolein**, which is then excreted in the urine. Acrolein is toxic to uroepithelial cells and can cause cell death and necrosis if allowed to be in contact with these cells for a prolonged period.

Hemorrhagic cystitis associated with nitrogen mustard-based chemotherapy can be **prevented** by aggressive hydration and the coadministration

Explanation

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Hemorrhagic cystitis associated with nitrogen mustard-based chemotherapy can be **prevented** by aggressive hydration and the coadministration of **mesna** (2-mercaptoethanesulfonate), a sulfhydryl compound that binds and inactivates the toxic metabolites of the chemotherapeutic agents in the urine.

(Choice A) Dexrazoxane is an iron-chelating agent that can help prevent anthracycline-induced (eg, doxorubicin) cardiotoxicity.

(Choice B) Filgrastim is a granulocyte colony-stimulating factor (G-CSF) analog used to stimulate the proliferation and differentiation of granulocytes in patients with neutropenia, as can occur after chemotherapy. This patient is afebrile, and her urinalysis is not suggestive of a urinary tract infection.

(Choice C) Leucovorin, or folinic acid, is a drug used in the treatment of methotrexate overdose. It also enhances the cytotoxic action of 5-fluorouracil (5-FU) and is used in combination with 5-FU in some cases of colorectal cancer.

(Choice E) Ondansetron inhibits serotonin 5-HT_3 receptors and is used primarily to treat nausea and vomiting following chemotherapy.

Educational objective:
Hemorrhagic cystitis during therapy with cyclophosphamide or ifosfamide is caused by the urinary excretion of the toxic metabolite acrolein. It can be prevented by aggressive hydration, bladder irrigation, and administration of mesna, a sulfhydryl compound that binds acrolein in the urine.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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had a similar episode 3 weeks ago and has been treated with warfarin since then. The patient has several other medical conditions and is taking all her medications as recommended. On examination, her temperature is 36.7 C (98 F), blood pressure is 120/60 mm Hg, pulse is 118/min, and respirations are 28/min. Pulse oximetry is 93% on room air. Laboratory results are notable for the following:

Coagulation studies

Prothrombin time (PT)	18 sec
International Normalized Ratio (INR)	1.6

The patient's INR is subtherapeutic compared to her target INR range of 2.0-3.0 with warfarin. This patient is most likely taking which of the following additional medications?

- A. Acetaminophen
- B. Amiodarone
- C. Aspirin
- D. Cimetidine
- E. Diazepam
- F. Indomethacin
- G. Metronidazole
- H. Oxycodone
- I. Phenytoin

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A 72-year-old woman is brought to the emergency department due to severe shortness of breath, tachypnea, and pleuritic-type chest pain. She had a similar episode 3 weeks ago and has been treated with warfarin since then. The patient has several other medical conditions and is taking all her medications as recommended. On examination, her temperature is 36.7 C (98 F), blood pressure is 120/60 mm Hg, pulse is 118/min, and respirations are 28/min. Pulse oximetry is 93% on room air. Laboratory results are notable for the following:

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- C. Aspirin
- D. Cimetidine
- E. Diazepam
- F. Indomethacin
- G. Metronidazole
- H. Oxycodone
- I. Phenytoin

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Coagulation studies

Prothrombin time (PT)	18 sec
International Normalized Ratio (INR)	1.6

The patient's INR is subtherapeutic compared to her target INR range of 2.0-3.0 with warfarin. This patient is most likely taking which of the following additional medications?

A. Acetaminophen (1%)
B. Amiodarone (5%)
C. Aspirin (10%)
D. Cimetidine (16%)
E. Diazepam (1%)
F. Indomethacin (1%)
G. Metronidazole (2%)
H. Oxycodone (0%)
✓ I. Phenytoin (59%)

Omitted
Correct answer
59%
04 secs
02/13/2020

Explanation

Drugs/supplements that affect warfarin metabolism (selected)	
CYP450 Inhibitors **↑ Warfarin effect** (↑ bleeding risk)	• Antibiotics (eg, metronidazole, macrolides) • Azole antifungals • Amiodarone • Cimetidine • Grapefruit juice
CYP450 Inducers **↓ Warfarin effect** (↓ in efficacy)	• Carbamazepine • Phenytoin • Phenobarbital • Rifampin • St. John's wort

CYP450 = cytochrome P-450.

This patient with pleuritic chest pain, dyspnea, tachypnea, tachycardia, and hypoxia most likely experienced a **recurrent pulmonary embolism** (PE) in the setting of a **subtherapeutic INR level**, reflecting decreased warfarin efficacy. **Warfarin** is an oral anticoagulant that inhibits activation of vitamin K–dependent clotting factors, particularly factor VII. As a result, warfarin administration leads to prolongation of the prothrombin time (PT) and INR (ratio of a patient's PT compared to a normal control). In patients with atrial fibrillation, deep venous thrombosis, or PE who are taking warfarin for anticoagulation, the dose is usually adjusted to achieve a target therapeutic INR range (generally 2.0-3.0).

Precise dosing of warfarin can be difficult due to its many interactions with other drugs that affect cytochrome P-450 activity, plasma protein binding, and/or gastrointestinal absorption. Warfarin elimination occurs primarily through hepatic metabolism by cytochrome P-450 enzymes. Drugs that **increase P-450 activity**, such as **phenytoin**, phenobarbital, and rifampin, **increase warfarin elimination** and decrease its anticoagulant activity (reflected as a subtherapeutic INR <2.0). Cholestyramine binds warfarin (and other drugs) in the intestine, thereby decreasing warfarin's therapeutic effect.

(Choices A, C, and F) When used concurrently with warfarin, aspirin and other nonsteroidal anti-inflammatory drugs such as indomethacin

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(Choices A, C, and F) When used concurrently with warfarin, aspirin and other nonsteroidal anti-inflammatory drugs such as indomethacin increase the risk of bleeding due to antiplatelet effects and gastrointestinal ulceration. These drugs can also displace warfarin from plasma protein binding sites (increasing the concentration of free warfarin). Acetaminophen can interfere with vitamin K metabolism and enhance the effect of warfarin.

(Choices B, D, and G) Both cimetidine and amiodarone inhibit the metabolism of warfarin, which can result in an increased PT/INR and bleeding risk. The interaction between amiodarone and warfarin is important because some patients with atrial fibrillation may be prescribed both medications. The commonly used antibiotics metronidazole and trimethoprim-sulfamethoxazole also inhibit warfarin metabolism.

(Choices E and H) Benzodiazepines and opiates usually do not interact significantly with warfarin.

Educational objective:
Rifampin, phenobarbital, and phenytoin are potent enhancers of the cytochrome P-450 pathway; concurrent use of warfarin with these medications results in decreased efficacy of warfarin. In contrast, cimetidine, amiodarone, and trimethoprim-sulfamethoxazole inhibit warfarin metabolism, increasing the risk of bleeding.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 45-year-old-woman comes to the office for follow-up 2 weeks after hospitalization for acute pyelonephritis. The patient was treated with morphine for pain and a course of broad-spectrum antibiotics, which she has completed. Her symptoms have now resolved. The patient also has a history of mechanical mitral valve replacement and takes warfarin. Physical examination shows no new findings. Her INR was 2.5 at the time of hospital discharge but is 6.2 today despite no change to warfarin dosage. Which of the following best explains the laboratory findings in this patient?

A. Decreased production of thromboxane A2

B. Disruption of intestinal bacterial flora

C. Formation of anticlotting factor antibodies

D. Increased cytochrome P-450 activity

E. Increased dietary vitamin K absorption

Submit

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- A. Decreased production of thromboxane A2 (1%)
- ✓ B. Disruption of intestinal bacterial flora (63%)
- C. Formation of anticlotting factor antibodies (3%)
- D. Increased cytochrome P-450 activity (28%)
- E. Increased dietary vitamin K absorption (3%)

Omitted
Correct answer
B

63%
Answered correctly

02 secs
Time Spent

04/14/2020
Last Updated

Explanation

Warfarin is a vitamin K antagonist that inhibits epoxide reductase in the liver, thereby preventing gamma carboxylation of vitamin K–dependent clotting factors (II, VII, IX, X). This creates an anticoagulant state that is reflected on laboratory assessment as a prolonged INR. Because the effect of warfarin is significantly altered by certain foods and medications, patients on long-term warfarin are at risk for subtherapeutic or **supratherapeutic INR** due to any of the following:

- Change in dietary vitamin K intake: Increase in dietary vitamin K increases the availability of vitamin K in the liver, which counters the

Explanation

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- Change in dietary vitamin K intake: Increase in dietary vitamin K increases the availability of vitamin K in the liver, which counters the inhibitory effect of warfarin on epoxide reductase. Therefore, patients on warfarin are advised to eat a consistent amount of vitamin K–containing foods (eg, leafy greens, brussels sprouts).
- **Disruption to intestinal flora:** Intestinal flora produce vitamin K as a byproduct of metabolism. Therefore, antibiotics that target gram-negative bacteria such as metronidazole, macrolides, and fluroquinolones can cause supratherapeutic INR due to destruction of vitamin K–producing bacteria in the gut. In this patient, the **administration of an antibiotic** (eg, ciprofloxacin) for pyelonephritis likely destroyed gram-negative bacteria in her gut, thereby **reducing vitamin K production** and causing a supratherapeutic INR.
- Alteration to cytochrome P450 2C9 activity: Several medications induce or inhibit cytochrome P450 2C9, which alters the speed of warfarin metabolism. For instance, phenytoin, carbamazepine, and rifampin increased cytochrome P450 2C9 activity, which can result in a subtherapeutic INR **(Choice D)**. In contrast, metronidazole, fluconazole, and amiodarone inhibit cytochrome P450 2C9 activity, which can result in a supratherapeutic INR.

(Choice A) Aspirin exerts an anticoagulation effect by inhibiting the release of thromboxane A2 by platelets, which subsequently reduces platelet aggregation. This can lead to prolonged bleeding time but does not increase INR.

(Choice C) Anticlotting factor antibodies can occasionally occur due to recent pregnancy, malignancy, or rheumatologic disease. Most cases involve inhibition of factor VIII, which leads to a bleeding diathesis and prolonged aPTT (not INR, which reflects PT). This patient with a recent infection treated with antibiotics is more likely to have supratherapeutic INR due to disruption of vitamin K production by intestinal flora.

(Choice E) Increased dietary vitamin K leads to a subtherapeutic INR due to increased vitamin K availability in the liver.

Educational objective:
Patients on warfarin who take antibiotics that target gram-negative microorganisms (eg, metronidazole, macrolides, fluroquinolones) can develop

- Change in dietary vitamin K intake: Increase in dietary vitamin K increases the availability of vitamin K in the liver, which counters the inhibitory effect of warfarin on epoxide reductase. Therefore, patients on warfarin are advised to eat a consistent amount of vitamin K–containing foods (eg, leafy greens, brussels sprouts).

- **Disruption to intestinal flora:** Intestinal flora produce vitamin K as a byproduct of metabolism. Therefore, antibiotics that target gram-negative bacteria such as metronidazole, macrolides, and fluroquinolones can cause supratherapeutic INR due to destruction of vitamin K–producing bacteria in the gut. In this patient, the **administration of an antibiotic** (eg, ciprofloxacin) for pyelonephritis likely destroyed gram-negative bacteria in her gut, thereby **reducing vitamin K production** and causing a supratherapeutic INR.

- Alteration to cytochrome P450 2C9 activity: Several medications induce or inhibit cytochrome P450 2C9, which alters the speed of warfarin metabolism. For instance, phenytoin, carbamazepine, and rifampin increased cytochrome P450 2C9 activity, which can result in a subtherapeutic INR **(Choice D)**. In contrast, metronidazole, fluconazole, and amiodarone inhibit cytochrome P450 2C9 activity, which can result in a supratherapeutic INR.

(Choice A) Aspirin exerts an anticoagulation effect by inhibiting the release of thromboxane A2 by platelets, which subsequently reduces platelet aggregation. This can lead to prolonged bleeding time but does not increase INR.

(Choice C) Anticlotting factor antibodies can occasionally occur due to recent pregnancy, malignancy, or rheumatologic disease. Most cases involve inhibition of factor VIII, which leads to a bleeding diathesis and prolonged aPTT (not INR, which reflects PT). This patient with a recent infection treated with antibiotics is more likely to have supratherapeutic INR due to disruption of vitamin K production by intestinal flora.

(Choice E) Increased dietary vitamin K leads to a subtherapeutic INR due to increased vitamin K availability in the liver.

Educational objective:
Patients on warfarin who take antibiotics that target gram-negative microorganisms (eg, metronidazole, macrolides, fluroquinolones) can develop supratherapeutic INR due to disruption of vitamin K–producing intestinal flora.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 62-year-old woman comes to the office due to a month of progressive right chest and back pain. The patient also noticed a right breast lump several months ago, which has grown over time. She has no prior medical issues, has not seen a physician for many years, and has had no cancer screenings. Physical examination reveals a hard, 5-cm right breast mass, enlarged axillary lymph nodes, and point tenderness along the right-sided ribs and 10th thoracic vertebra. Biopsy of the breast mass shows hormone receptor–positive, HER2-negative, invasive ductal carcinoma. Skeletal survey demonstrates lytic lesions of the ribs and thoracic vertebrae. As part of the treatment regimen, the patient receives a medication that is a potent inhibitor of cyclin-dependent kinase. Which of the following is the most likely dose-limiting toxicity of this medication?

- A. Bone marrow suppression
- B. Cardiomyopathy
- C. Immune-mediated toxicity
- D. Peripheral neuropathy
- E. Sensorineural hearing loss

Submit

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- ✓ A. Bone marrow suppression (65%)
- B. Cardiomyopathy (18%)
- C. Immune-mediated toxicity (5%)
- D. Peripheral neuropathy (6%)
- E. Sensorineural hearing loss (4%)

Omitted
Correct answer
A

65%
Answered correctly

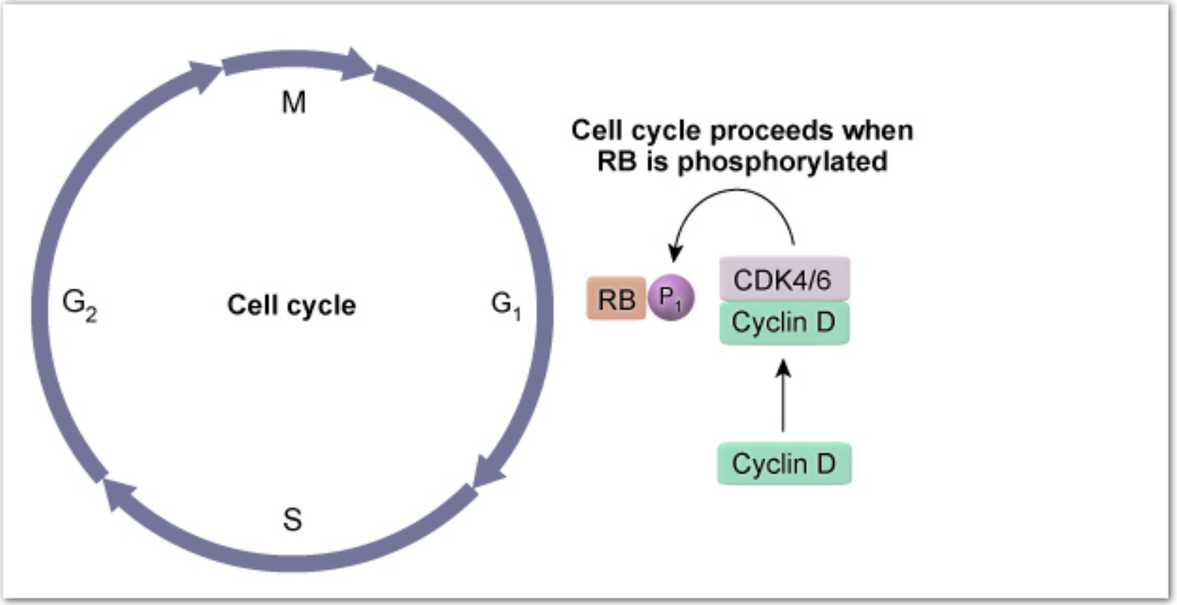
02 secs
Time Spent

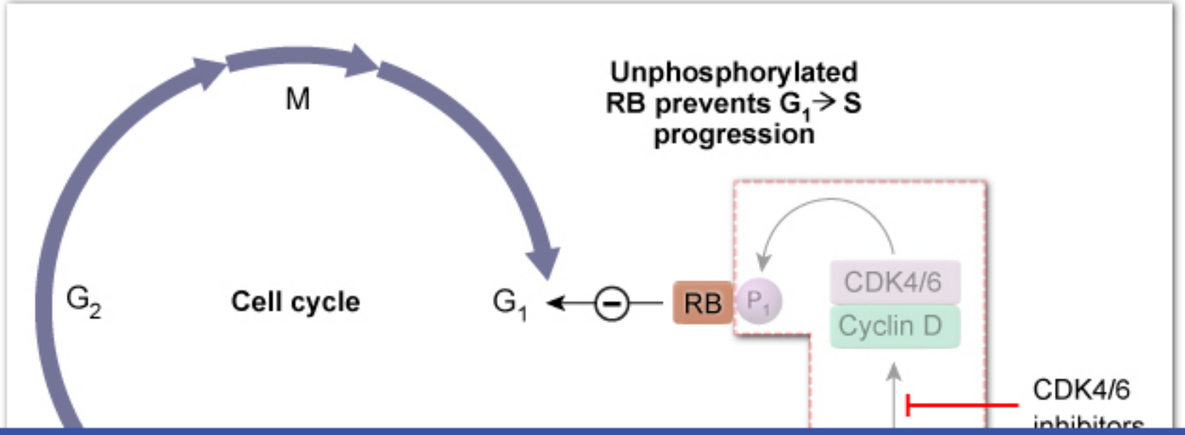
01/29/2020
Last Updated

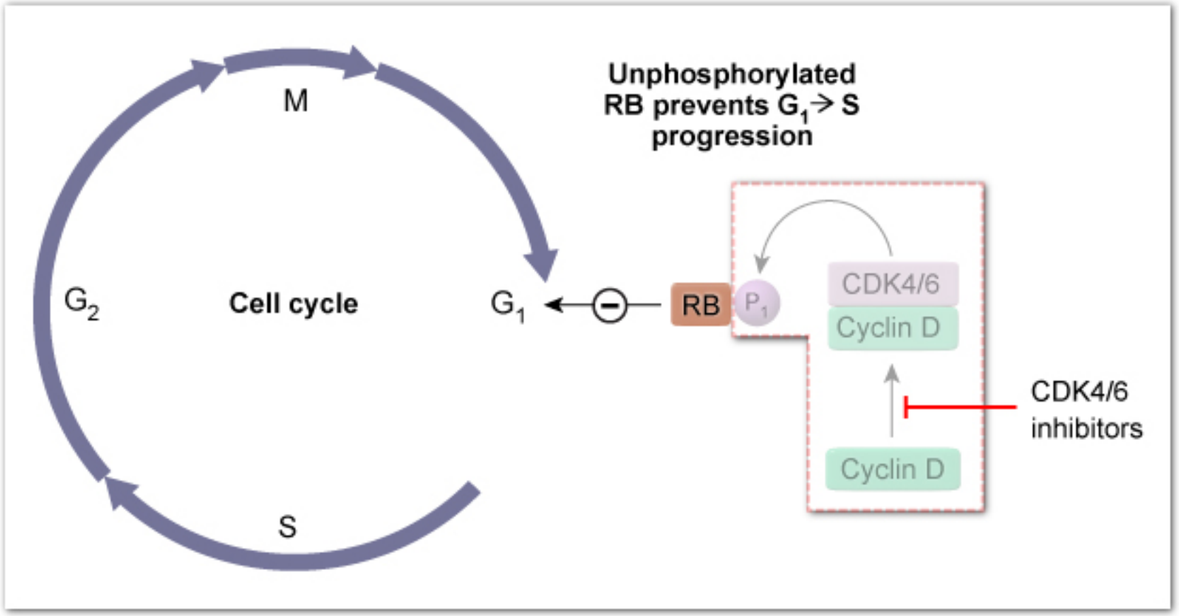
Explanation

CDK4/6 inhibitors

CDK4/6 inhibitors







RB = retinoblastoma tumor suppressor protein; **CDK** = cyclin-dependent kinase.

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The cellular growth cycle consists of 4 distinct phases: G_1, S, G_2, and M. Progression through the phases is controlled by surveillance systems (checkpoints) that interrupt the cell cycle and/or induce apoptosis if cells do not meet the requirements to progress forward:

- The transition from $G_1 \rightarrow S$ (initiation of DNA replication) is controlled by a combination of cell size and nutrient status, exposure to growth factors, and proper surveillance and repair of damaged DNA.
- At the $G_2 \rightarrow M$ transition, the cell again checks for DNA damage and repairs replication errors before they can be passed on to daughter cells during mitosis. An additional spindle checkpoint ensures that duplicated chromosomes separate appropriately during cell division.

Cyclin-dependent kinases (CDKs) 4 and 6 control cell cycle progression from $G_1 \rightarrow S$. These CDKs are activated by cyclin D and subsequently inhibit the retinoblastoma tumor suppressor protein, leading to the upregulation of transcriptional factors that **progress the cell cycle** to S phase. Many cancers exploit this crucial checkpoint and achieve unregulated cellular growth via cyclin D amplification (or inactivating mutations to *retinoblastoma* gene).

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CDK 4/6 inhibitors (eg, palbociclib) can be used to block the cyclin D binding site on CDK, which results in decreased CDK 4/6 activation, increased activity of the retinoblastoma tumor suppressor protein, and cell cycle arrest. Although CDK 4/6 inhibitors are generally well tolerated, they often **inhibit** cellular replication in other **rapidly dividing cells**, particularly hematologic cells in the **bone marrow**. This can result in treatment-limiting hematologic side effects such as neutropenia, leukopenia, and anemia.

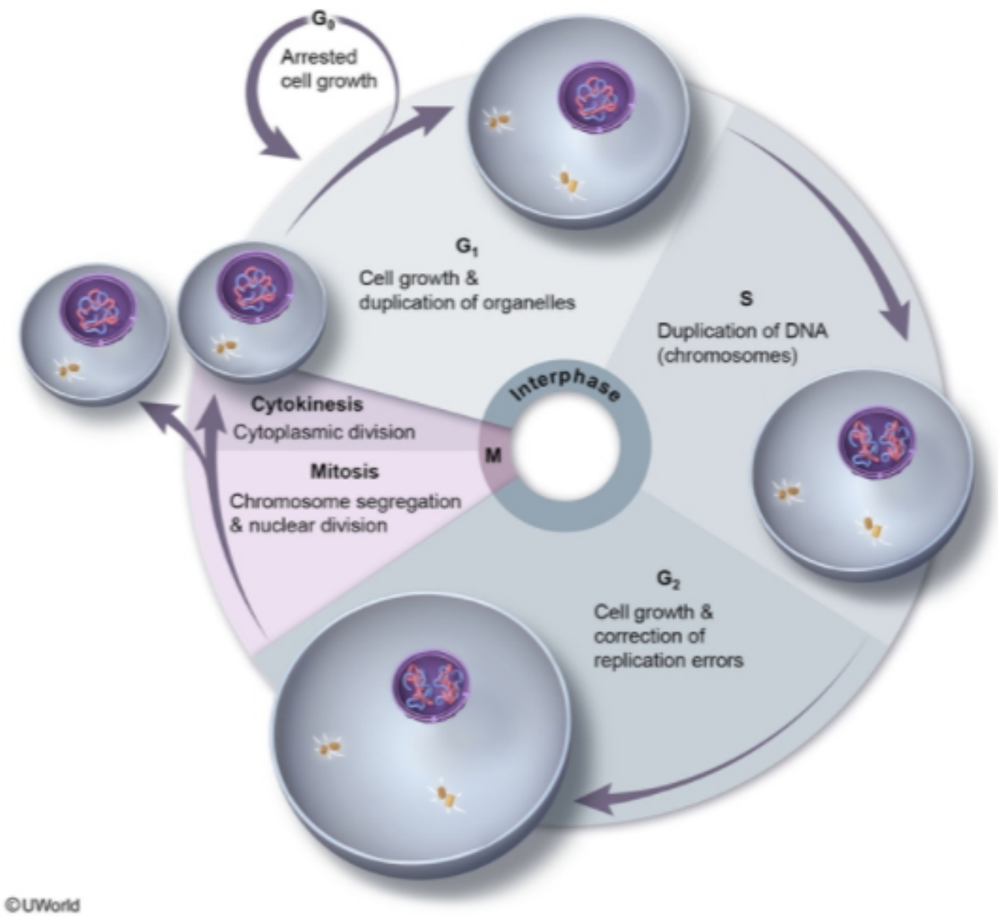
(Choice C) Immunotherapy that targets PD-1, PD-L1, and CTLA-4 enhances the immune response against cancer and is often used in the treatment of malignant melanoma. The major side effects of these medications are autoimmune-related adverse events, including skin, liver, gastrointestinal, and endocrine inflammation.

(Choices B, D, and E) CDK 4/6 inhibitors do not generally cause adverse side effects in cells that are arrested in G_0, such as myocytes, cochlear hair cells, or neurons. Cardiomyopathy is a common side effect of anthracyclines (eg, doxorubicin) and HER2 antibodies (eg, trastuzumab). Sensorineural hearing loss can be seen with platinum-based chemotherapy (eg, cisplatin). Peripheral neuropathy is a common side effect of vincristine and bortezomib.

Educational objective:
Cyclin-dependent kinases (CDKs) 4/6 regulate the movement of cells from $G_1 \rightarrow S$ phase. Cancers often have mutations that enhance the activity or downstream effects of CDK 4/6, which contribute to unregulated cellular growth. Inhibitors to CDK 4/6 can be used to treat certain forms of

S

Exhibit Display



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References

- Palbociclib in hormone-receptor-positive advanced breast cancer.

Pharmacology	Hematology & Oncology	Cell cycle
Subject	System	Topic

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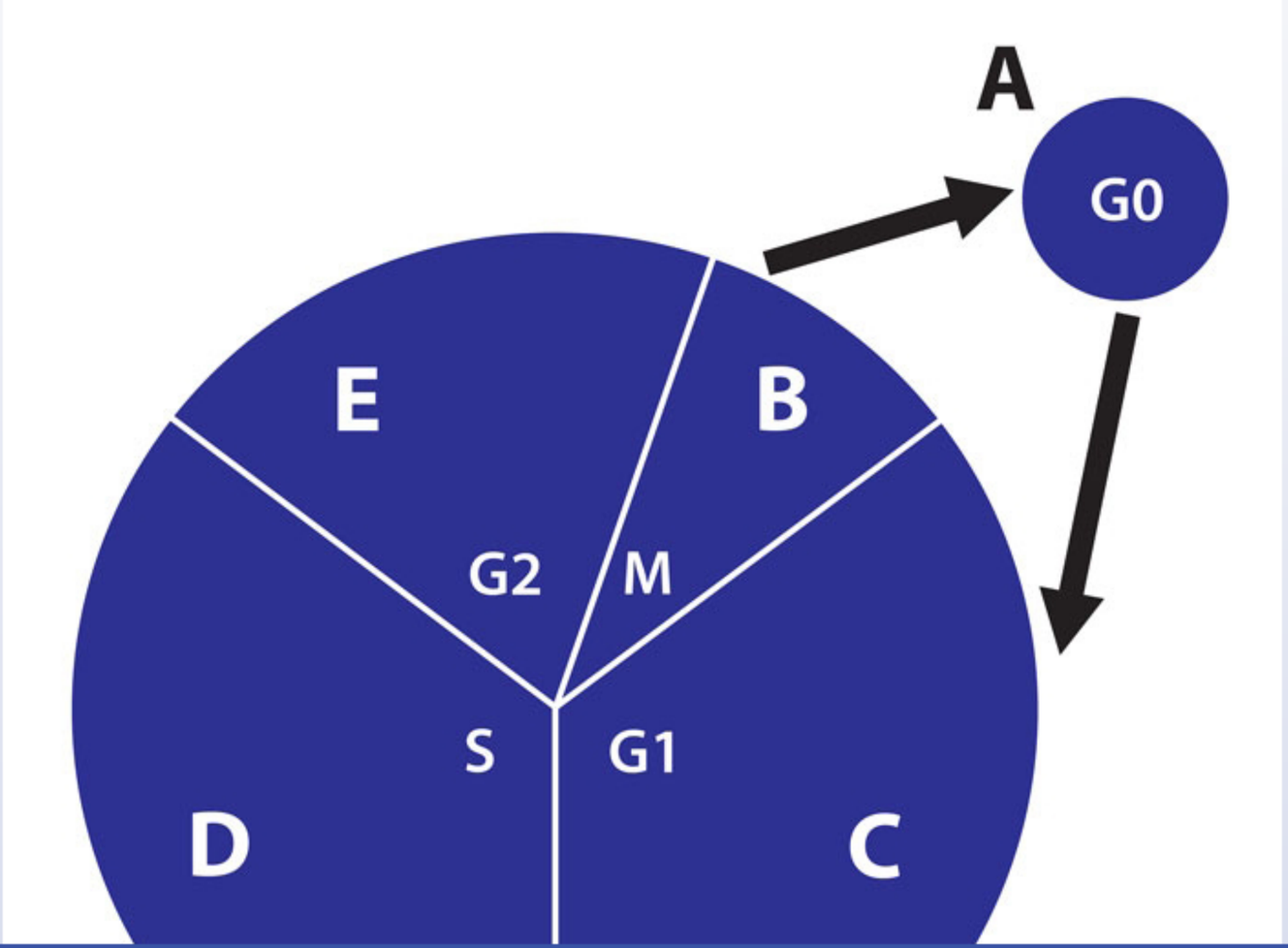
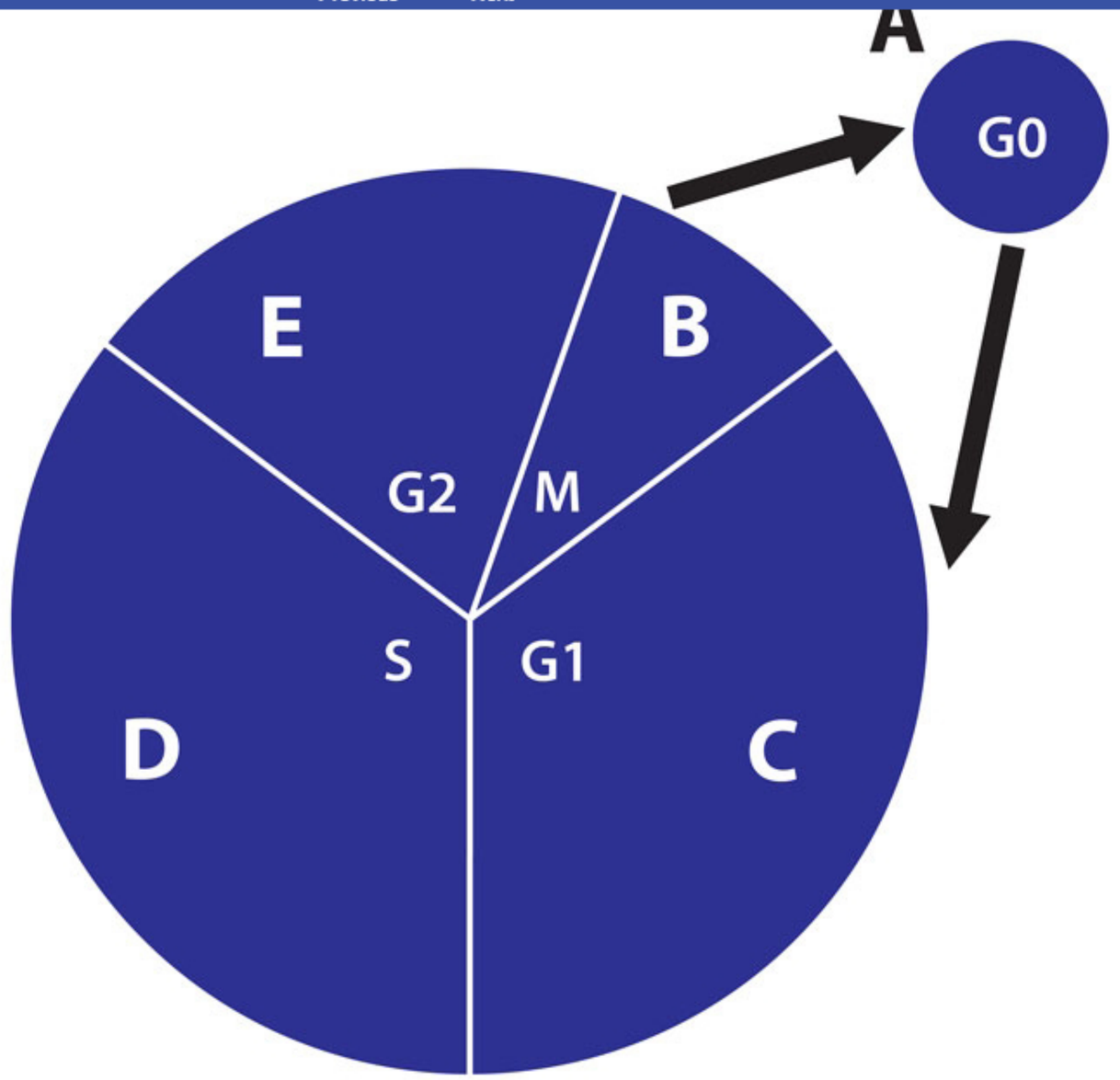
A 61-year-old man comes to the office due to tingling of his hands and feet. He has a history of diffuse large B cell lymphoma and has received several cycles of systemic chemotherapy with a regimen that includes cyclophosphamide, doxorubicin, and vincristine. Neurologic examination is notable for a symmetric distal neuropathy in a "stocking and glove" distribution. His electrolytes and fasting blood glucose are normal. The drug responsible for this patient's neurologic symptoms causes cell cycle arrest during which of the following stages?




A
G0
E
B
G2
M
S
G1
D
C

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A. A

B. B

C. C

D. D

E. E

Submit

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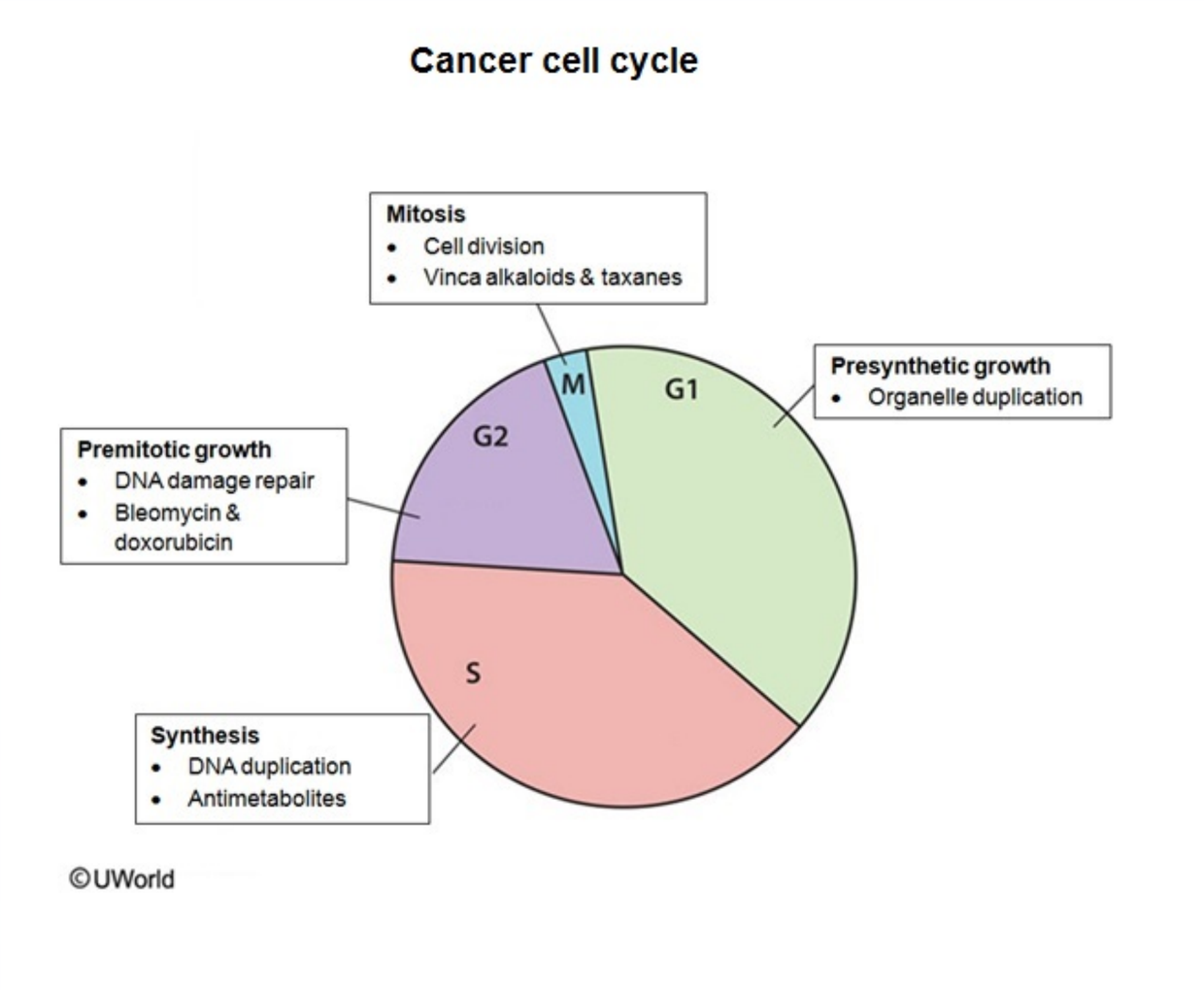
A. A (3%)
B. B (68%)
C. C (13%)
D. D (12%)
E. E (2%)

Omitted
Correct answer

68%
Answered correctly

07 secs
Time Spent

06/01/2020
Last Updated



This patient with diffuse large B cell lymphoma (most common type of **non-Hodgkin lymphoma**) has peripheral neuropathy likely due to vincristine. The **vinca alkaloids** (eg, vincristine, vinblastine) function by **inhibiting microtubule formation**. Specifically, these agents bind to β-tubulin, thereby preventing polymerization of microtubule proteins. This causes cell cycle-specific cytotoxicity during the **M phase** of the cell cycle

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Of the vinca alkaloids, **vincristine** is most classically associated with neurotoxicity, which is often dose-related and most commonly presents as **peripheral neuropathy**. Neurotoxicity likely results from disruption of neuronal microtubules, which are responsible for transporting organelles and other cellular products between the neuronal cell body and the axon terminals.

(Choices A, C, D, and E) The following is a description of the phases of the cell cycle:

- G1: Cells in this phase prepare the building blocks for DNA synthesis.
- G0: This is a resting stage.
- S: DNA replication occurs during this phase. Topoisomerase I and II inhibitors (eg, etoposide, irinotecan), as well as some antimetabolites (eg, methotrexate, 5-fluorouracil), function during this phase.
- G2: In this phase, DNA is checked for errors and corrections are made if possible. If corrections cannot be made, then apoptosis will result unless loss-of-function mutations to the genes controlling this process are present, a condition frequently encountered in tumor cells. Chemotherapeutic agents active at this stage include drugs that intercalate with DNA and induce free radical formation. Examples are bleomycin (can cause lung fibrosis) and doxorubicin (can cause cardiomyopathy).
- M: Division occurs during this stage. Vinca alkaloids and taxanes are specific to this phase.

Some chemotherapeutic agents are cell-cycle nonspecific; these include cyclophosphamide, an alkylating agent with side effects that include bone marrow suppression, alopecia, and hemorrhagic cystitis.

Educational objective:
The vinca alkaloids are cell cycle-specific agents that prevent proper separation of chromosomes into daughter cells during the M phase of the cell cycle. The main dose-limiting side effect of vincristine is neurotoxicity, which commonly manifests as peripheral neuropathy.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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An elderly patient is diagnosed with aggressive non-Hodgkin's lymphoma. The tumor cells are shown to stain strongly for the CD20 marker. Which of the following biologic agents can be added to this patient's chemotherapy regimen to help improve the treatment response?

A. Infliximab
B. Rituximab
C. Interleukin-2
D. Imatinib
E. Abciximab

Submit

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- A. Infliximab (6%)
- ✓ B. Rituximab (72%)
- C. Interleukin-2 (5%)
- D. Imatinib (11%)
- E. Abciximab (3%)

Omitted
Correct answer
B

72%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

The class of treatments known as biologic response modifiers (BRMs) includes antibodies, cytokines and other substances intended to restore or induce the immune system's ability to overcome disease. All of the answer choices here are BRMs.

The patient described above has a lymphoma that expresses surface CD20, a B-cell marker. Rituximab is a monoclonal antibody used in lymphoma immunotherapy that specifically targets the CD20 surface immunoglobulin.

Another monoclonal antibody used in cancer treatment is trastuzumab (Herceptin), which is used in the treatment of breast cancer.

(Choice A) Infliximab is a chimeric (human/murine) IgG1 monoclonal antibody to TNF-alpha. This medication has had a significant impact on the management of rheumatoid arthritis. Infliximab is also used to treat ankylosing spondylitis and fistulizing Crohn's disease.

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(Choice C) Interleukin-2 is a cytokine that regulates the activation and differentiation of T-cells to aid in tumor cell destruction. It is FDA-approved for the treatment of renal cell carcinoma and melanoma.

(Choice D) Diagnosis of CML requires the presence of the Philadelphia chromosome or the BCR/ABL fusion gene. Imatinib mesylate is a potent inhibitor of the BCR/ABL protein tyrosine kinase. It inhibits the cellular proliferation of BCR/ABL-expressing cells without inducing apoptosis. This oral medication has dramatically changed the management of CML since its introduction.

(Choice E) Abciximab is a chimeric mouse-human monoclonal antibody against the platelet GP IIb/IIIa receptor. It works by blocking the final step in platelet aggregation. Abciximab is often administered during angioplasty in patients with acute coronary syndrome.

Educational Objective:
Rituximab is a monoclonal antibody directed against the CD20 antigen. Its introduction has improved the prognosis of some lymphomas.

Pharmacology	Hematology & Oncology	Nonhodgkin lymphoma
Subject	System	Topic

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A 70-year-old man develops progressive fatigue and easy bruising. He has had unintentional weight loss and episodic fevers. Physical examination shows splenomegaly and enlarged lymph nodes in the cervical, axillary, and inguinal regions. Complete blood count reveals anemia, thrombocytopenia, and leukocytosis. Peripheral blood smear shows an increased number of small, mature-appearing, abnormal lymphocytes, which express CD20 and kappa light chains. During treatment, the patient receives an agent that directly binds and inhibits BCL-2 protein. Which of the following is the most likely effect of this therapy on the abnormal cells?

- A. Accumulation of ubiquitinated intracellular proteins
- B. Greater susceptibility to cytotoxic T cells
- C. Increased activation of caspases
- D. Increased single-strand DNA breaks
- E. Interruption of cell growth in S phase
- F. Targeting of antibody-dependent cellular cytotoxicity

Submit

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- A. Accumulation of ubiquitinated intracellular proteins (3%)
- B. Greater susceptibility to cytotoxic T cells (3%)
- ✓ C. Increased activation of caspases (78%)
- D. Increased single-strand DNA breaks (1%)
- E. Interruption of cell growth in S phase (9%)
- F. Targeting of antibody-dependent cellular cytotoxicity (3%)

Omitted
Correct answer
C

78%
Answered correctly

01 min, 18 secs
Time Spent

02/01/2020
Last Updated

Explanation

This patient's lymphadenopathy, splenomegaly, and increased number of mature lymphocytes in the blood that express B-cell markers ($CD20^+$, kappa light chains) indicate **chronic lymphocytic leukemia** (CLL). This disease is characterized by the progressive accumulation of **mature B cells** in hematopoietic tissues (leading to anemia, thrombocytopenia, lymphadenopathy, and splenomegaly) and peripheral blood (leading to leukocytosis) due to genetic mutations that lengthen B-cell survival.

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In most cases of CLL, B-cell survival is promoted by the **overexpression of BCL-2** on the mitochondrial membrane. BCL-2 is an **antiapoptotic** protein that prevents stress signals from triggering the intrinsic apoptotic cascade, which is mediated by the release of cytochrome c from the mitochondria and the subsequent activation of caspases. Treatment of CLL with **BCL-2 inhibitors** (eg, venetoclax) makes tumor cells more sensitive to stress signals (eg, chemotherapy) by **increasing the activation of caspases**, which leads to cell death.

(Choice A) Bortezomib, a proteasome inhibitor that prevents the destruction of ubiquinated intracellular proteins, can be used against neoplasms that generate excessive amounts of protein (eg, multiple myeloma).

(Choice B) Because cancer cells produce new antigens (neoantigens) not seen in normal cells, they generally have mutations that allow them to evade cytotoxic T-cell detection. Immune checkpoint inhibitors, such as antibodies against PD-1 (eg, pembrolizumab) or CTLA-4, prevent cancer cells from evading cytotoxic T-cell detection.

(Choice D) Olaparib inhibits poly-ADP ribose polymerase, the enzyme that mediates the repair of single-strand DNA breaks. It is often used to treat breast, ovarian, or prostate cancer in individuals with BRCA mutations.

(Choice E) Many forms of chemotherapy target rapidly dividing cells by inhibiting DNA replication during S phase (eg, purine analogs). BCL-2 does not mediate DNA replication or repair.

(Choice F) Rituximab is a monoclonal antibody against the B-cell surface marker CD20. Although it is often used for CLL, it mediates cell death by binding to the B-cell surface (antibody-mediated cytotoxicity).

Educational objective:
Chronic lymphocytic leukemia is associated with overexpression of BCL-2, an anti-apoptotic protein, on the mitochondrial membrane. Treatment with a BCL inhibitor causes cancer cell death by promoting cytochrome c release from the mitochondria, which subsequently activates caspases.

References

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References

- The Bcl-2 apoptotic switch in cancer development and therapy.

Pharmacology	Hematology & Oncology	Bcl 2
Subject	System	Topic

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A 56-year-old Caucasian male with non-Hodgkin lymphoma is undergoing systemic chemotherapy. Vincristine is a part of the regimen, and you suspect accidental overdose of that agent. Which of the following would you most expect in this patient?

- A. Finger numbness and tingling
- B. Burning on urination and urgency
- C. Leg swelling and orthopnea
- D. Dry cough and exertional dyspnea
- E. Tarry stool and fatigue
- F. Abdominal pain and jaundice

Submit

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- ✓ A. Finger numbness and tingling (76%)
- B. Burning on urination and urgency (4%)
- C. Leg swelling and orthopnea (3%)
- D. Dry cough and exertional dyspnea (3%)
- E. Tarry stool and fatigue (3%)
- F. Abdominal pain and jaundice (7%)

Omitted
Correct answer
A

76%
Answered correctly

01 sec
Time Spent

02/03/2020
Last Updated

Explanation

Vincristine causes neurotoxicity by interfering with microtubule formation in nerve axons. Patients with vincristine toxicity most commonly complain of peripheral neuropathy, and neurotoxicity is the dose-limiting side effect **(Choice A)**. All vinca alkaloids (vincristine, vinblastine) inhibit microtubule polymerization after binding to β-tubulin. Inhibition of microtubule formation prevents synthesis of the mitotic spindle in dividing cells. Without the mitotic spindle, replicated chromosomes are unable to align and segregate into their respective daughter cells during mitosis. This leads to failure of division and cell death. Vinca alkaloid agents are thus M-phase specific agents.

(Choice B) Burning on urination and urgency may be seen with cyclophosphamide- or ifosfamide-induced hemorrhagic cystitis.

Vincristine causes neurotoxicity by interfering with microtubule formation in nerve axons. Patients with vincristine toxicity most commonly complain of peripheral neuropathy, and neurotoxicity is the dose-limiting side effect **(Choice A)**. All vinca alkaloids (vincristine, vinblastine) inhibit microtubule polymerization after binding to β-tubulin. Inhibition of microtubule formation prevents synthesis of the mitotic spindle in dividing cells. Without the mitotic spindle, replicated chromosomes are unable to align and segregate into their respective daughter cells during mitosis. This leads to failure of division and cell death. Vinca alkaloid agents are thus M-phase specific agents.

(Choice B) Burning on urination and urgency may be seen with cyclophosphamide- or ifosfamide-induced hemorrhagic cystitis.

(Choice C) Leg swelling and orthopnea are symptoms of congestive heart failure. Of the chemotherapeutic agents, doxorubicin, an anthracycline antibiotic and a chemotherapeutic intercalating agent, is most commonly associated CHF.

(Choice D) Dry cough and exertional dyspnea may be seen with bleomycin, which is classically associated with pulmonary toxicity. Bleomycin specifically causes a progressive pulmonary fibrosis that can lead to death in a minority of patients.

(Choice E) Tarry stool and fatigue may be seen with any chemotherapeutic agent that affects rapidly-dividing cells, but are most classically associated with alkylating agents. These agents cause death in both the rapidly-dividing tumor cells, and in other groups of cells that have a high turn-over rate, like hair, skin, and the mucosa of the GI system. Tarry stool, also called melena, is most commonly due to an upper GI bleed.

(Choice F) Abdominal pain and jaundice may be seen with mercaptopurine use. Mercaptopurine is an S-phase specific purine analogue that is associated with cholestasis and hepatitis in a fair proportion of patients. Chronic methotrexate ingestion, used in rheumatoid arthritis for anti-inflammatory purposes, is also associated with cirrhosis.

Educational Objective:
Neurotoxicity is the dose-limiting side effect of vincristine therapy. This toxicity results from failure of microtubule polymerization in neuronal axons. Other notable adverse effects classically associated with chemotherapeutic agents include pulmonary fibrosis and flagellate skin discoloration with bleomycin use; congestive heart failure with doxorubicin; and hemorrhagic cystitis with cyclophosphamide.

Pharmacology	Hematology & Oncology	Chemotherapy
Subject	System	Topic

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A 52-year-old man comes to the emergency department (ED) due to 2 hours of burning substernal pain. Before coming to the ED, he took several tablets of antacid at home without any relief. The patient's other medical problems include hypertension and hyperlipidemia. His temperature is 36.7 C (98 F), blood pressure is 160/90 mm Hg, and pulse is 92/min. Cardiovascular examination shows normal S1 and S2 without any murmurs. There is no abdominal tenderness. ECG shows ST-segment depression in leads II, III, and aVF. Troponin is 0.06 ng/mL (normal <0.01 ng/mL). As part of this patient's treatment, enoxaparin therapy is initiated. This drug is expected to bind to which of the following substances in this patient's blood?

- A. Antithrombin III
- B. Fibrin
- C. Plasminogen
- D. Protein C
- E. Prothrombin

Submit

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- ✓ A. Antithrombin III (73%)
- B. Fibrin (4%)
- C. Plasminogen (3%)
- D. Protein C (1%)
- E. Prothrombin (16%)

Omitted
Correct answer
A

73%
Answered correctly

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Time Spent

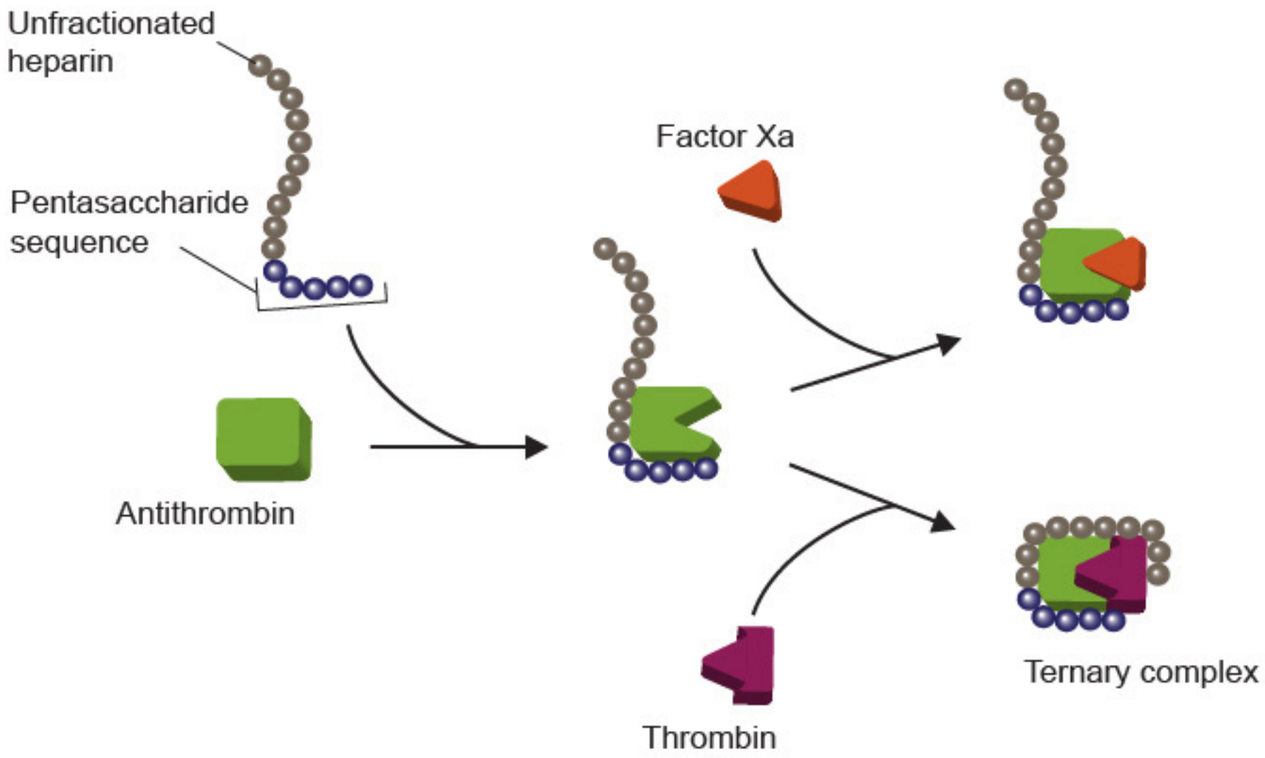
06/01/2020
Last Updated

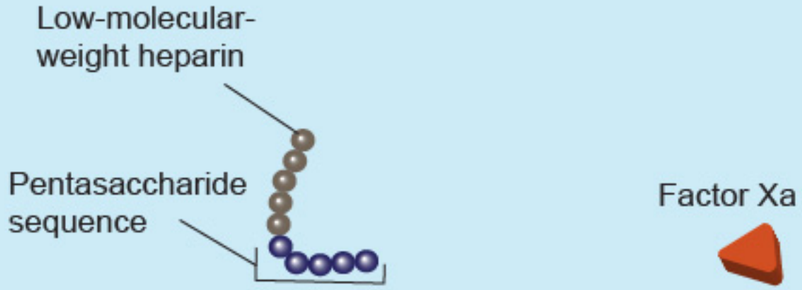
Explanation

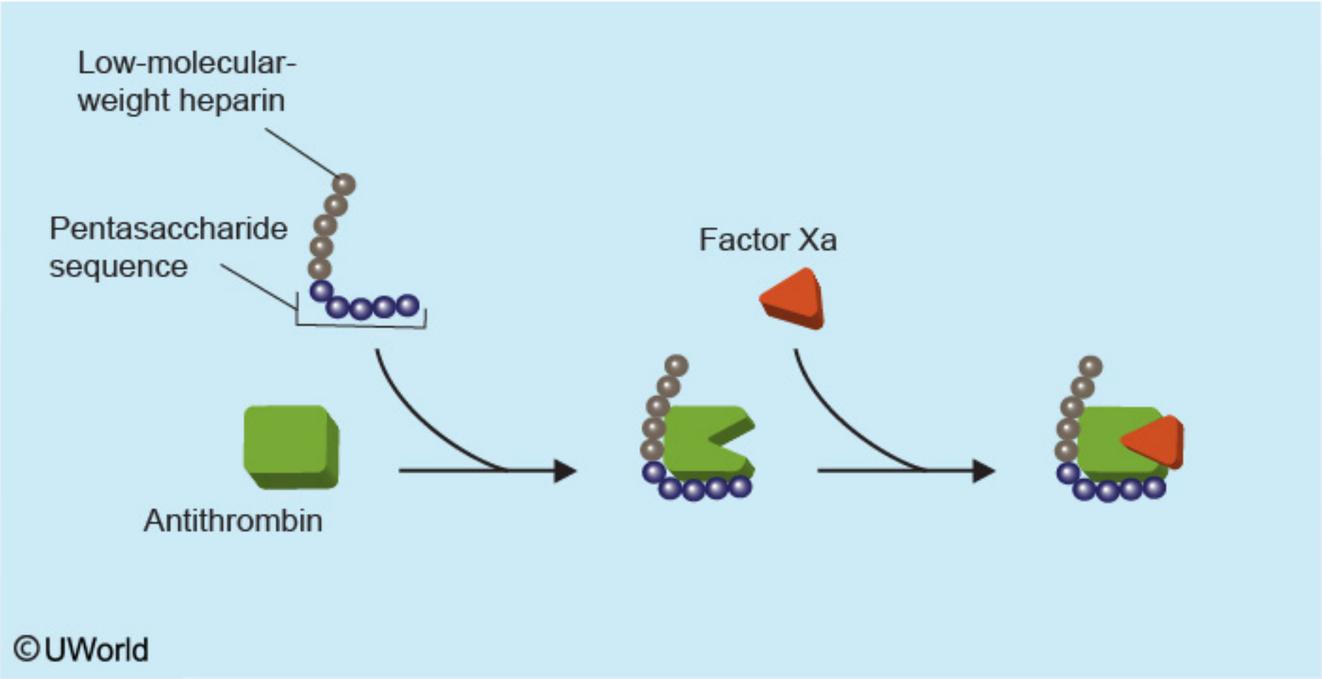
Heparin's mechanism of action

Unfractionated heparin

Heparin's mechanism of action







This patient with chest pain, ST depressions, and mild troponin elevation appears to be experiencing a myocardial infarction. **Enoxaparin** is a form of low-molecular-weight heparin (LMWH) that, like heparin, functions by binding **antithrombin III** (AT III) via a pentasaccharide sequence. Once activated, AT III binds to **factor Xa** and stops factor Xa from converting prothrombin to thrombin. Less thrombin is produced, resulting in an anticoagulant effect.

Unfractionated heparin has more molecules than LMWH, allowing it to bind factor Xa and thrombin; it is more effective than LMWH in inactivating thrombin.

(Choices B and C) Tissue plasminogen activator (t-PA) converts plasminogen to plasmin. Plasmin functions to break down fibrin, resulting in thrombolysis. Because t-PA can only bind plasminogen strongly in the presence of fibrin, its thrombolytic action is clot specific.

(Choice D) Protein C and protein S are endogenous antithrombotic molecules that are also vitamin K-dependent. Due to their shorter half-lives in the circulation, these molecules are depleted first during initiation of warfarin therapy, causing a transient procoagulant state. For this reason,

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(Choice D) Protein C and protein S are endogenous antithrombotic molecules that are also vitamin K-dependent. Due to their shorter half-lives in the circulation, these molecules are depleted first during initiation of warfarin therapy, causing a transient procoagulant state. For this reason, patients are typically treated with heparin or LMWH during initiation of warfarin therapy.

(Choice E) Prothrombin (factor II) is a vitamin K-dependent clotting factor. This factor, along with factors VII, IX, and X, is depleted by warfarin. LMWHs inhibit prothrombin production (through factor X inhibition), but they do not directly bind prothrombin.

Educational objective:
Enoxaparin is a low-molecular-weight heparin (LMWH) that functions like heparin in that it binds and activates antithrombin III (AT III). Activated AT III binds to factor Xa and stops factor Xa from converting prothrombin to thrombin. Due to its fewer number of molecules, LMWH acts primarily on factor Xa, not thrombin.

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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An 18-year-old man with a history of recurrent hemarthroses and severe mucosal bleeding due to hemophilia A comes to the office for follow-up. He has had occasional breakthrough bleeding despite receiving prophylactic factor VIII infusions. Testing reveals the patient now has inhibitor alloantibodies against factor VIII, and factor replacement products can no longer be used. Treatment with a novel medication that prevents bleeding by mimicking the function of factor VIII is initiated. This medication most likely works by which of the following mechanisms?

A. Anchoring platelets to subendothelial collagen

B. Binding factor VIIa to mediate factor X activation

C. Cleaving von Willebrand factor multimers

D. Cross-linking fibrin molecules

E. Linking factors IXa and X to create activated X (Xa)

Submit

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A. Anchoring platelets to subendothelial collagen (8%)

B. Binding factor VIIa to mediate factor X activation (14%)

C. Cleaving von Willebrand factor multimers (6%)

D. Cross-linking fibrin molecules (1%)

✓ E. Linking factors IXa and X to create activated X (Xa) (68%)

Omitted
Correct answer
E

68%
Answered correctly

02 secs
Time Spent

04/13/2020
Last Updated

Explanation

Hemophilia A is an X-linked, recessive bleeding disorder caused by mutations to the gene that encodes clotting **factor VIII**. Factor VIII is part of the intrinsic coagulation cascade; it acts as a bridging protein that brings together the catalytic component of **factor IXa** (the protease) with **factor X** (the substrate), thereby amplifying formation of factor Xa, which promotes fibrin clots.

Patients with hemophilia A have severe reductions in factor VIII and are unable to form fibrin clots at sites of minor trauma, leading to potentially life-threatening hemarthroses and mucosal bleeding. Treatment with factor VIII replacement products (eg, factor VIII concentrate from plasma) can prevent or treat bleeding in these patients. However, long-term efficacy is often limited by the formation of neutralizing antibodies **(factor VIII**

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Emicizumab, a bispecific monoclonal antibody, mimics the normal physiologic function of factor VIII and can be used to prevent or treat bleeding in patients who have factor VIII inhibitors. This antibody has 2 binding sites; one site binds to factor IXa and the other binds to factor X, which brings them into **close proximity** and allows factor IXa to cleave factor X into its active form (Xa).

(Choice A) Von Willebrand factor, a large glycoprotein produced by the endothelium, aids platelet clot formation by binding platelets to subendothelial collagen at sites of injury. It is also a carrier protein for factor VIII; therefore, patients with Von Willebrand factor deficiency often have mild or moderate reductions in factor VIII. However, serious bleeding (eg, hemarthroses) is very uncommon.

(Choice B) Activation of factor X to Xa can also occur via the extrinsic (tissue factor pathway) in response to tissue trauma. In this case, factor VIIa in combination with tissue factor activates factor X. This pathway does not require factor VIII and is unaffected in those with hemophilia A.

(Choice C) Ultra-large von Willebrand factor multimers produced by the endothelium are cleaved to smaller subunits by the metalloprotease ADAMTS13. Loss of ADAMTS13 activity leads to thrombotic thrombocytopenic purpura.

(Choice D) Factor XIIIa cross-links loose fibrin molecules into a dense network, thereby forming stable fibrin clots. Factor XIIIa is unaffected in those with hemophilia A.

Educational objective:
Hemophilia A is an X-linked disorder associated with a deficiency of factor VIII. Emicizumab—a bispecific, monoclonal antibody—mimics the activity of factor VIII by binding to both factor IXa and factor X, bringing them into close proximity to allow for factor X activation.

References

- Emicizumab prophylaxis in patients who have hemophilia A without inhibitors.

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A 68-year-old man is brought to the emergency department due to sudden-onset, severe right lower extremity pain. On physical examination, the right leg is pale and cold to the touch with absent distal pulses. Cardiac auscultation reveals an irregular tachycardia, and ECG shows atrial fibrillation. Right lower extremity ultrasonography reveals an arterial embolus. Intravenous heparin infusion is initiated. This medication is most likely to cause which of the following coagulation changes?

	Thrombin time	Partial thromboplastin time (PTT)	Activity of factor Xa
A.	No change	Prolonged	Decreased
B.	No change	Prolonged	Increased
C.	Prolonged	No change	Increased
D.	Prolonged	Prolonged	No change
E.	Prolonged	Prolonged	Decreased

Submit

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	Thrombin time	Partial thromboplastin time (PTT)	Activity of factor Xa
A.	No change (35%)	Prolonged	Decreased
B.	No change (3%)	Prolonged	Increased
C.	Prolonged (2%)	No change	Increased
D.	Prolonged (6%)	Prolonged	No change
✓ E.	Prolonged (51%)	Prolonged	Decreased

Omitted
Correct answer
E

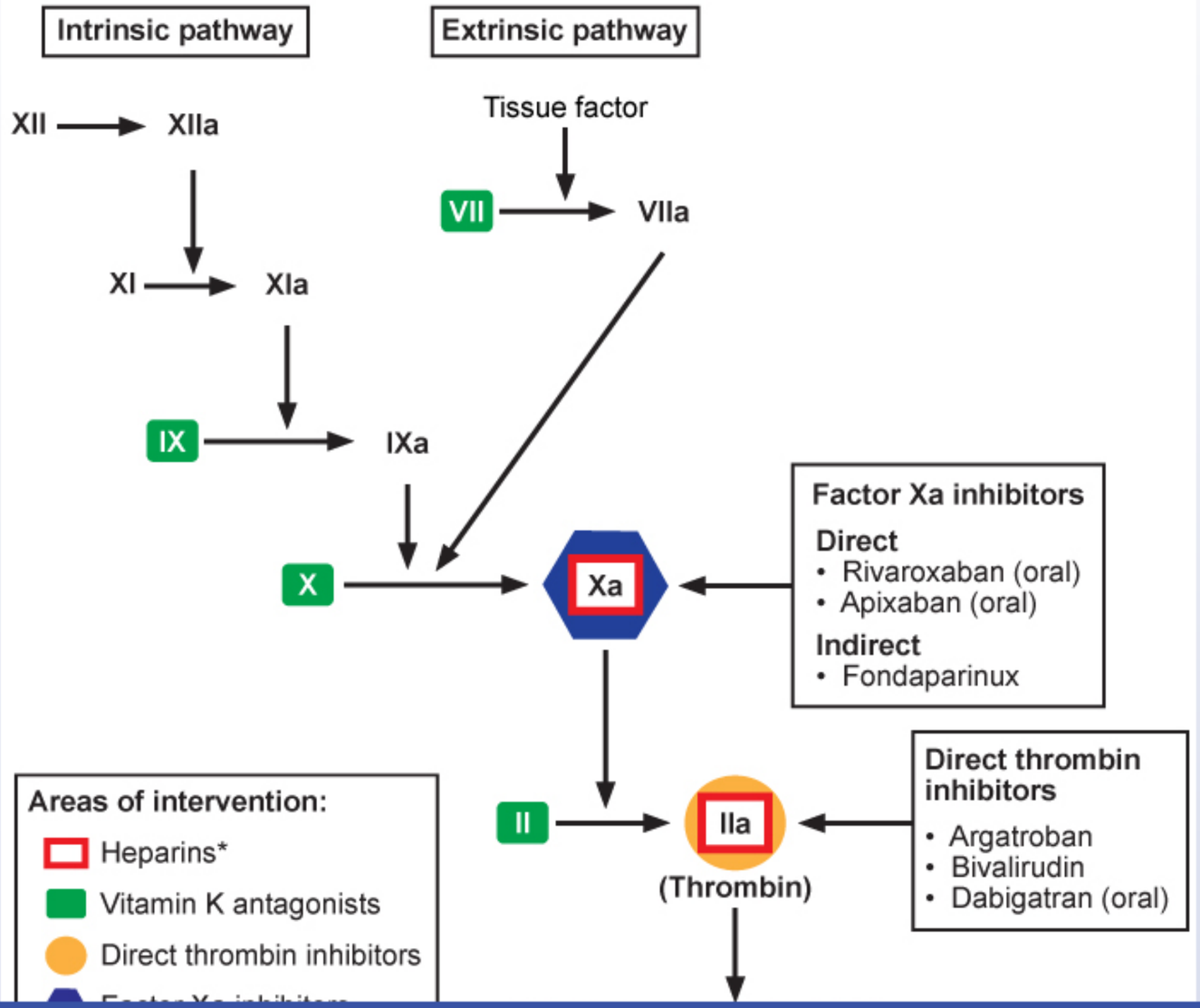
51%
Answered correctly

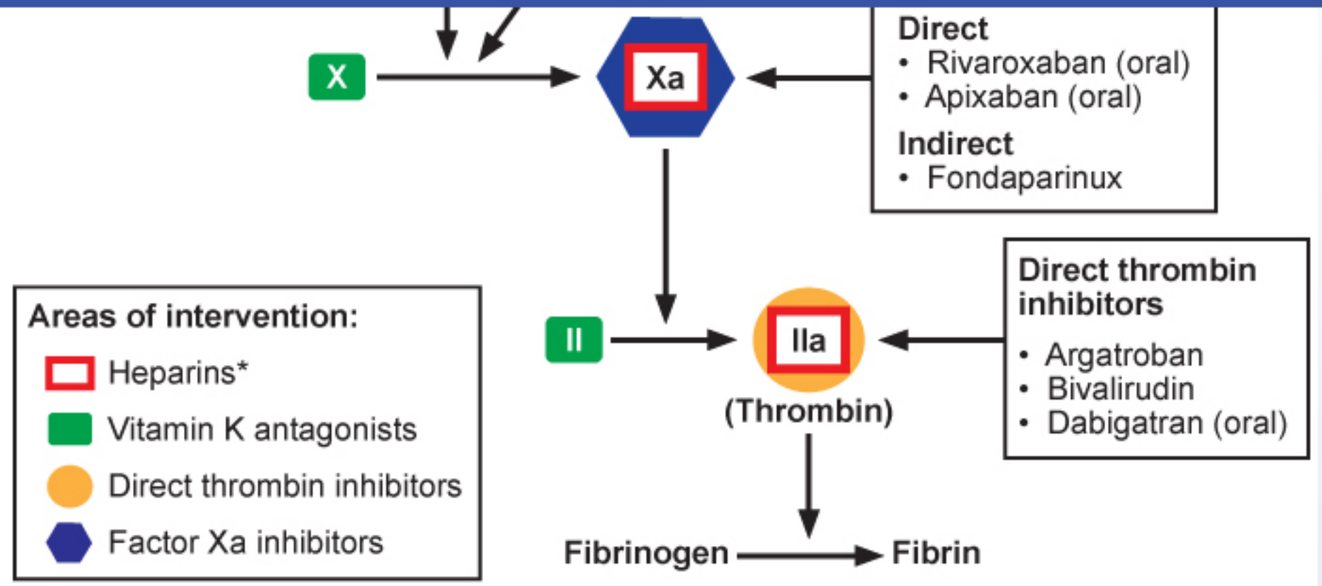
02 secs
Time Spent

04/14/2020
Last Updated

Explanation

Anticoagulants & their mechanism of action





*Major mechanism of action; antithrombin III has some inhibition on all activated coagulation factors.
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Heparin is an endogenous anticoagulant that exerts its effect **indirectly** by binding to **antithrombin III** (AT), a serine protease inhibitor that irreversibly neutralizes clotting factors. Heparin binding alters the shape of AT, which converts it from a **slow to rapid inactivator** of clotting factors and increases its activity **>1,000 fold**.

Although AT neutralizes a number of clotting factors in the intrinsic pathway, its anticoagulant effect primarily stems from the inactivation of **factor Xa** and **thrombin**. Therefore, patients who receive heparin products typically have the following coagulation changes:

- **Prolonged thrombin time:** Thrombin inactivation is strongest with unfractionated heparin infusion because the length of heparin chains in this formulation are longer, which inactivates thrombin more rapidly. Although low-molecular-weight heparin formulations contain shorter chain heparin molecules, they also inactivate thrombin but to a lesser extent.
- **Decreased activity of factor Xa:** All forms of heparin (eg, unfractionated, low molecular weight, fondaparinux) have strong activity against factor Xa. Antifactor Xa activity is usually monitored to determine when adequate anticoagulation is achieved.

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- **Prolonged partial thromboplastin time** (PTT): Heparin primarily inhibits the intrinsic and final common clotting pathway; therefore, PTT is prolonged.

Unlike heparin medications, which exert their anticoagulation effects broadly through the activation of AT, direct oral anticoagulants inhibit a single enzyme in the coagulation cascade, such as thrombin (eg, dabigatran) or factor Xa (eg, rivaroxaban).

Educational objective:
Heparin is an indirect anticoagulant that alters the shape of antithrombin (AT) III, thereby converting it from a slow to rapid inactivator of clotting factors. Because AT primarily neutralizes factor Xa and thrombin, patients on heparin have decreased factor Xa activity and prolonged thrombin time/partial thromboplastin time. In contrast, direct oral anticoagulants specifically target a single enzyme in the coagulation cascade, such as thrombin (eg, dabigatran) or factor Xa (eg, rivaroxaban).

Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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Pharmacology	Hematology & Oncology	Anticoagulants
Subject	System	Topic

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A 23-year-old man is evaluated for excessive bruising since childhood. He says some of his family members "bleed easily" and sometimes require blood transfusions. Temperature is 36.7 C (98.1 F). Physical examination is unremarkable. Complete blood cell count is unremarkable. Platelet aggregometry is abnormal. Genetic testing identifies a defect in a platelet surface glycoprotein receptor that normally binds fibrinogen to support platelet aggregation. The abnormal glycoprotein receptor found in this patient is most likely targeted by which of the following medications?

- A. Abciximab
- B. Argatroban
- C. Aspirin
- D. Clopidogrel
- E. Dabigatran
- F. Heparin
- G. Warfarin

Submit

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- ✓ A. Abciximab (66%)
- B. Argatroban (4%)
- C. Aspirin (2%)
- D. Clopidogrel (21%)
- E. Dabigatran (2%)
- F. Heparin (2%)
- G. Warfarin (0%)

Omitted
Correct answer
A

66%
Answered correctly

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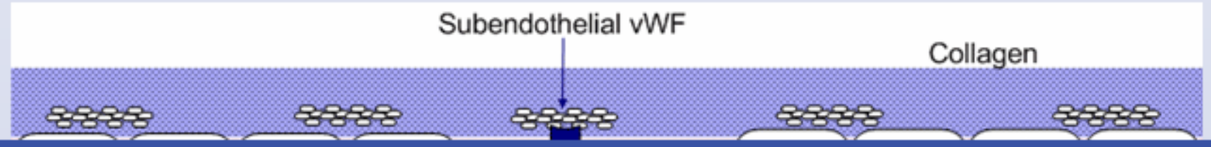
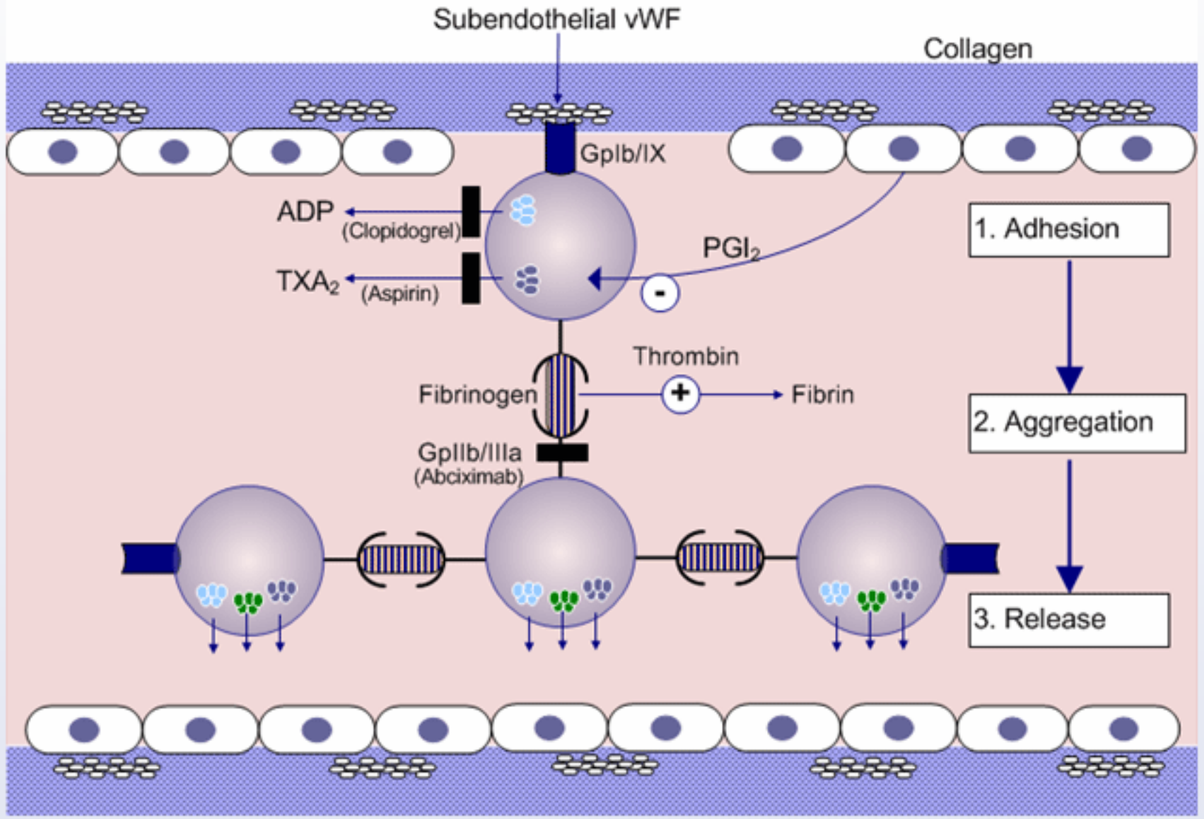
Time Spent

05/05/2020
Last Updated

Explanation





This patient likely has Glanzmann thrombasthenia, an autosomal recessive disorder that is caused by a deficient or defective **glycoprotein (GP) IIb/IIIa** on platelet surfaces and that typically presents in childhood with mucocutaneous bleeding. Peripheral smear shows no platelet clumping (an important clue for diagnosis).

Platelets are responsible for formation of platelet plugs that stop bleeding from injured vessels (**primary hemostasis**). Vessel wall injury exposes the subendothelial collagen and matrix. Platelet attachment to exposed collagen is strengthened by GP Ib binding to von Willebrand factor on the vessel wall. The resulting platelet activation leads to the following:

- Release of mediators (eg, ADP, thromboxane A2 [TXA2]) into circulation, which in turn activates other platelets

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- Release of mediators (eg, ADP, thromboxane A2 [TXA2]) into circulation, which in turn activates other platelets
- Conformational structural change of **GP IIb/IIIa** on platelet surfaces; this allows thousands of copies of GP IIb/IIIa to bind **fibrinogen**, thereby forming a **platelet plug**.

Abciximab, a **GP IIb/IIIa receptor antagonist**, inhibits binding of this receptor to fibrinogen. Abciximab and other GP IIb/IIIa inhibitors are useful for treatment of unstable angina and acute coronary syndrome, particularly in patients undergoing percutaneous coronary intervention.

(Choices B, E, F, and G) Argatroban (used in heparin-induced thrombocytopenia) and dabigatran (used in atrial fibrillation or venous thromboembolism) are direct thrombin inhibitors. Heparin potentiates antithrombin III activity, leading to inactivation of thrombin and factor Xa; warfarin prevents K-mediated carboxylation of several coagulation factors. All these medications have anticoagulant effects.

(Choices C and D) Aspirin, a cyclooxygenase (COX)-1 and 2 inhibitor, inhibits TXA2 (via platelet COX acetylation), thereby preventing platelet aggregation. Clopidogrel inhibits platelet aggregation by blocking P2Y12 on platelet ADP receptors.

Educational objective:
Abciximab is a blocker of glycoprotein (GP) IIb/IIIa receptor, which normally promotes platelet binding to fibrinogen. GP IIb/IIIa is either deficient or defective in patients with Glanzmann thrombasthenia.

Pharmacology	Hematology & Oncology	Glanzmann thrombasthenia
Subject	System	Topic

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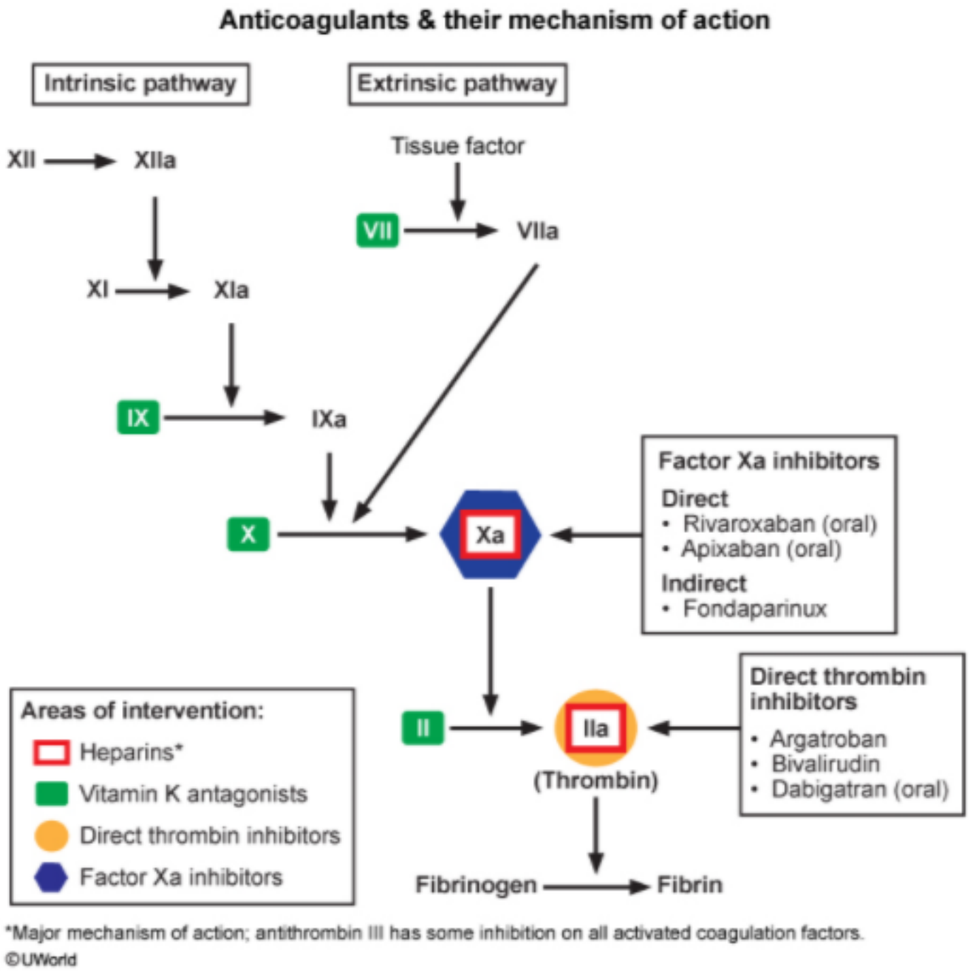

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